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Total Synthesis and Biological Evaluation of Neodysiherbaine A and Analogues

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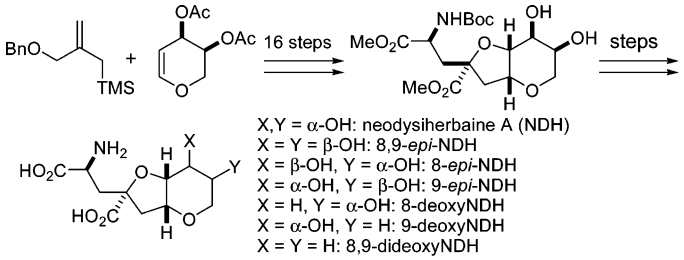

Dysiherbaine (**1**) and its congener neodysiherbaine A (**2**) are naturally occurring excitatory amino acids with selective and potent agonistic activity for ionotropic glutamate receptors. We describe herein the total synthesis of **2** and its structural analogues **3**−**8**. Advanced key intermediate **16** was employed as a branching point to assemble a series of these analogues **3**−**8** with respect to the C_8 and C_9 functionalities, which would not have been accessible through manipulations of the natural product itself. The synthesis of key intermediate **16** features (i) stereocontrolled *C*-glycosylation to set the C_6 stereocenter, (ii) concise synthesis of the bicyclic ether skeleton through chemo- and stereoselective dihydroxylation of the *exo*-olefin and stereoselective epoxidation of the *endo*-olefin, followed by epoxide ring opening/5-*exo* ring closure, and (iii) catalytic asymmetric hydrogenation of enamide ester to construct the amino acid appendage. A preliminary biological evaluation of analogues for their in vivo toxicity against mice and binding affinity for glutamate receptors showed that both the type and stereochemistry of the C_8 and C_9 functional groups affected the subtype selectivity of dysiherbaine analogues for members of the kainic acid receptor family.

Introduction

Glutamate receptors play a central role in the mammalian central nervous system (CNS), not only in excitatory neurotransmission but also in complex brain functions such as learning and memory. Glutamate receptors are broadly divided into ionotropic and metabotropic receptors. Ionotropic glutamate receptors are further subdivided into three subtypes on the basis of their pharmacological preference toward selective agonists: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainate, and *N*-methyl-D-aspartic acid (NMDA) receptors.[1] Molecular cloning studies demonstrated that ionotropic glutamate receptors are encoded by at least six NMDA (NR1, NR2A−D, and NR3A), four AMPA (GluR1−4), and five kainate (GluR5−7, KA1, and KA2) receptor genes.[2] Understanding the complex roles that ionotropic glutamate receptors play in physiological

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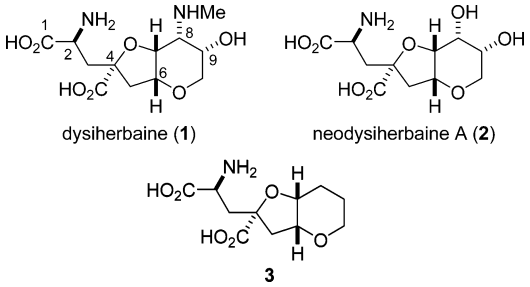

FIGURE 1. Structures of dysiherbaine (**1**), neodysiherbaine A (**2**), and simplified analogue **3**.

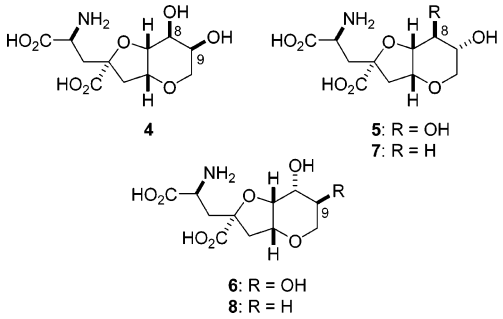

FIGURE 2. Structures of dysiherbaine analogues **4**−**8**.

and pathological processes in the brain has been facilitated by the presence of selective pharmacological agents. However, pharmacological characterization of kainate receptors has for many years been hampered by the lack of selective ligands, both agonists and, particularly, antagonists.[3]

Dysiherbaine (**1**), isolated from the Micronesian sponge *Dysidea herbacea*, is a novel excitatory amino acid with potent convulsant activity[4] (Figure 1). The unprecedented molecular structure consists of a *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamic acid substructure. Dysiherbaine activates neuronal AMPA and kainate receptors, with a higher affinity for kainate receptors, but shows no detectable affinity for NMDA receptors.[5] Pharmacological characterization of the affinity of dysiherbaine for recombinant GluR5, GluR6, and KA2 kainate receptor subunits revealed that it had extremely high affinity for GluR5 or GluR6 but very low affinity for KA2 subunits, which produced unusual biophysical behavior from heteromeric kainate receptors.[6]

Neodysiherbaine A (**2**), isolated as a minor congener from the same sponge, differs from **1** in the C_8 functional group[7] (Figure 1) and is also a selective agonist for AMPA and kainate receptors. Most recently, we characterized the pharmacological action of neodysiherbaine A and a simplified synthetic analogue, **3**,[8] on glutamate receptors.[9] These studies revealed that neodysiherbaine A is similar to dysiherbaine in its pharmacological activity on kainate receptors, albeit with slightly different binding affinities for individual receptor types. In contrast, compound **3**, lacking the C_8 and C_9 functional groups, was a selective, competitive antagonist for GluR5-containing kainate receptors. In addition, homology modeling of kainate receptor subunits generated a conceptual framework for understanding the interaction between the C_8 and C_9 functional groups and residues in the ligand-binding domains that confer selectivity and specificity to the marine toxins.[9]

Due to these unusual pharmacological properties of dysiherbaines and their potent epileptogenic activity, these excitatory amino acids and their designed analogues are anticipated to serve as useful tools for understanding the structure and functions of ionotropic glutamate receptors in the CNS. Therefore, dysiherbaine and neodysiherbaine A have attracted a great deal of attention as synthetic targets, and seven total syntheses[7,10] and several synthetic approaches[11] have been described to date.

To reveal further the detailed structure−activity relationship profiles of dysiherbaines, we set out to develop a flexible route to a series of dysiherbaine analogues. We describe herein the details of a concise total synthesis of **2** and its structural analogues 8,9-*epi*-neodysiherbaine A (**4**),[12] 8-*epi*-neodysiherbaine A (**5**), 9-*epi*-neodysiherbaine A (**6**), 8-deoxyneodysiherbaine A (**7**), and 9-deoxyneodysiherbaine A (**8**) (Figure 2) from a common key intermediate. These analogues, easily accessible through efficient synthesis, allowed us to test the hypothesis that the C_8 and C_9 functional groups are the critical determinants of pharmacological activity of dysiherbaines. The preliminary biological evaluation described herein revealed that both the type and stereochemistry of these functional groups strongly affected the subtype selectivity of dysiherbaine analogues for members of the kainate receptor family.

Results and Discussion

Overall Synthetic Strategy. We have previously reported the synthesis of **4** via a key intermediate, **16**,[12] which was settled on a branching point for a flexible entry into the dysiherbaine analogues not accessible from the natural product itself. The key features of the synthesis of **16** involved (i) stereoselective *C*-glycosylation of allylsilane **10**[13] with di-*O*-acetyl-L-arabinal (**9**)[14] to set the C_6 stereocenter, (ii) chemoselective oxidation of bisolefin **11**, (iii) epoxide ring opening/5-*exo* ring closure of

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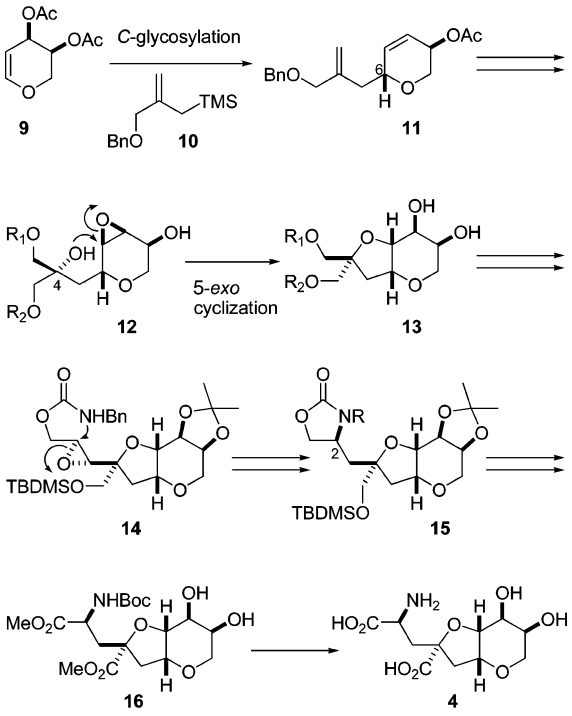
SCHEME 1. Our First Total Synthesis of 8,9-*epi*-Neodysiherbaine A (4)

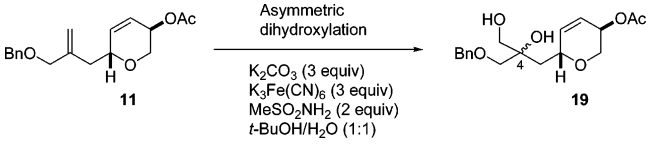


12 to form the bicyclic ring skeleton **13**, and (iv) construction of the amino acid side chain through stereoselective introduction of the C_2 amino group following the procedure of Kishi et al.[15] (**14** → **15**) (Scheme 1).

While highly concise to construct the bicyclic ether skeleton, this first-generation route required a multistep sequence of reactions for the C_2 amino group. Accordingly, we decided to explore an alternative approach for the efficient synthesis of the amino acid appendage. In this context, we focused on an asymmetric hydrogenation of enamide esters, which has been recently utilized for the synthesis of various functionalized amino acid derivatives.[16,17] Thus, the key intermediate **16** was envisioned to be prepared by catalytic asymmetric hydrogenation of the precursor enamide ester **17**, which, in turn, could be readily derived from alcohol **18** through oxidation followed by Horner−Wadsworth−Emmons (HWE) olefination (Scheme 2).

We first reinvestigated chemo- and diastereoselective oxidation of the *exo*-olefin within **11** under Sharpless asymmetric dihydroxylation conditions.[18] In the previous study,[12] oxidation of **11** with AD-mix-α ($CH_3SO_2NH_2$, *t*-BuOH/H_2O, 0 °C → room temperature) proceeded in a completely chemoselective manner to produce diol **19** in 85% yield; however, the diastereoselectivity proved to be low (ca. 1.3:1) by 500 MHz ^{1}H NMR (Table 1, entry 1). The stereochemistry at the C_4 stereocenter was

TABLE 1. Asymmetric Dihydroxylation of Diene 11



entry	osmium source[a]	ligand[b]	time (h)	yield (%)	dr[c]
1	AD-mix-α		12	85	1:1.3
2	AD-mix-β		12	quantitative	1.2:1
3	$K_2OsO_2(OH)_2$	$(DHQD)_2AQN$	12	58	3:1
4[d,e]	OsO_4	$(DHQD)_2AQN$	3	80	3:1
5	$K_2OsO_2(OH)_2$	$(DHQD)_2PYR$	12	78	1:2.3
6	$K_2OsO_2(OH)_2$	$(DHQ)_2PYR$	12	59	2.3:1

[a] A 1 mol % concentration of $K_2OsO_2(OH)_2$ was used. [b] A 10 mol % concentration of ligand was used. [c] Determined by 500 MHz ^{1}H NMR. [d] Performed on a gram scale. [e] A 5 mol % concentration of OsO_4 was used.

assigned at a later stage. The use of pseudoenantiomeric reagent AD-mix-β resulted in reversed but poor diastereoselectivity (entry 2). The highest diastereoselectivity (dr = 3:1) was observed when $(DHQD)_2AQN$[19] was used as a ligand (entry 3), and these conditions showed good reproducibility even on a gram scale (entry 4). When the $(DHQD)_2PYR$[20] ligand was used, the diastereoselectivity was reversed with a moderate ratio (entry 5), and the selectivity was reversed again by changing the ligand to $(DHQ)_2PYR$ (entry 6). The diastereomeric mixture thus obtained in entry 4 was carried forward without separation through the subsequent transformations.

Selective monosilylation of diol **19** was performed under standard conditions (TBDMSOTf, triethylamine, CH_2Cl_2) to afford the corresponding TBDMS ether **20** (Scheme 3). After methanolysis of the acetyl group (95%), treatment of the resultant allylic alcohol with *m*-chloroperbenzoic acid (*m*-CPBA) led exclusively to the β-epoxide **21**. When the crude epoxide **21** was subjected to purification by flash chromatography on silica gel, epoxide ring opening by an intramolecular attack of the tertiary alcohol occurred in a 5-*exo*-trig mode, leading to bicyclic ether **22** in high yield. After protection of the diol as the acetonide (85%), the benzyl group of the resultant **23** was removed under hydrogenolysis to afford alcohols **24a** and **24b** in 75% and 20% yield, respectively, which were readily separable by flash column chromatography. Thus, the synthesis of the bicyclic ether skeleton was realized in only seven steps from **9**. In addition, both alcohols **24a** and **24b** are considered to be potentially identical compounds, just being different in the position of the TBDMS protection. Therefore, these compounds were expected to be transformed to the single compound in a convergent manner.

Introduction of an Amino Acid Appendage. Oxidation of the major alcohol **24a** to the corresponding acid by a two-step sequence (SO_3·pyridine/DMSO and $NaClO_2$ oxidations) followed by esterification with trimethylsilyldiazomethane ($TMSCHN_2$) provided methyl ester **25** in 85% overall yield (Scheme 4). At this stage, the stereochemistry at the C_4 position was determined by NOE experiments as shown. Removal of the TBDMS group with TBAF gave the desired alcohol **18** in 85% yield.

On the other hand, the minor diastereomeric alcohol **24b** was also converted to **18** as depicted in Scheme 5. Thus, protection

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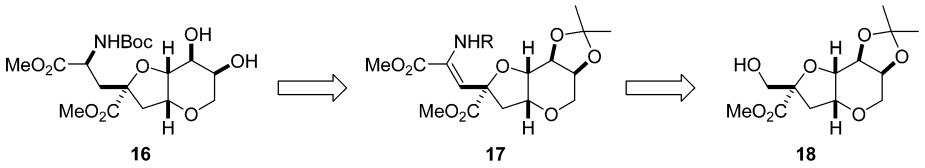
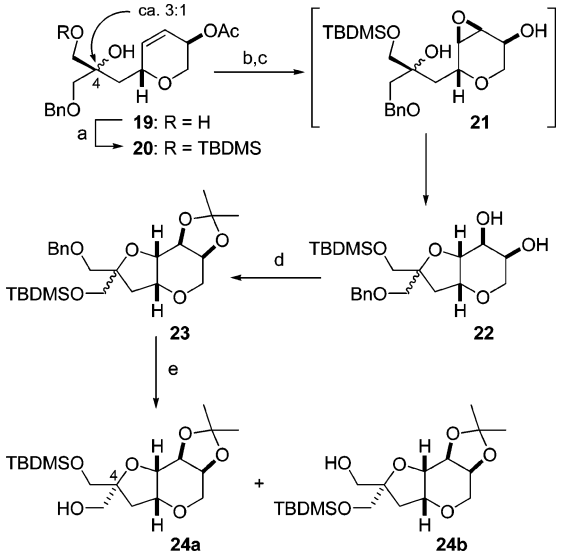
SCHEME 2. New Approach for Key Intermediate 16

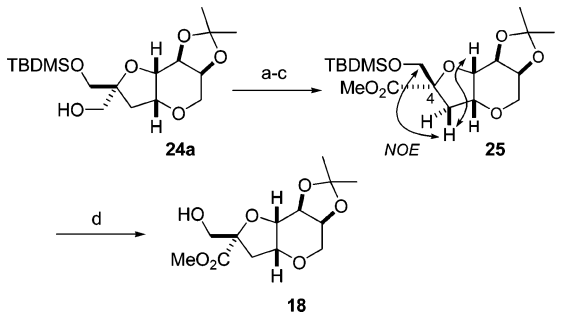


SCHEME 3[a]



[a] Reagents and conditions: (a) TBDMSOTf, Et_3N, DMAP, CH_2Cl_2, rt, 85%; (b) K_2CO_3, MeOH, rt, 95%; (c) *m*-CPBA, CH_2Cl_2/pH 7 phosphate buffer, 0 °C → rt, then silica gel, 89%; (d) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 0 °C, 85%; (e) H_2, Pd/C, hexane, rt, (**24a**) 75%, (**24b**) 20%.

SCHEME 4[a]

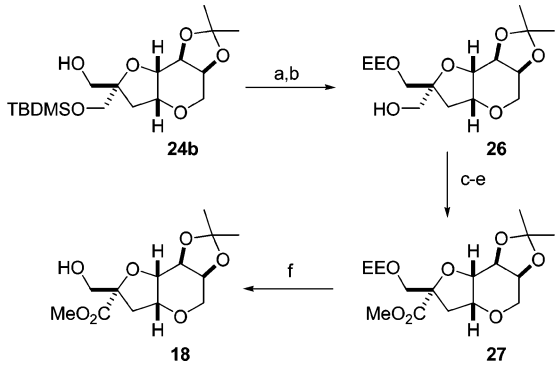


[a] Reagents and conditions: (a) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C; (b) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O, rt; (c) $TMSCHN_2$, MeOH, rt, 85% (three steps); (d) TBAF, THF, rt, 85%.

of **24b** as the ethoxyethyl (EE) ether followed by removal of the TBDMS group provided alcohol **26**. The primary hydroxy group was oxidized to the corresponding carboxylic acid by a two-step procedure and esterified with $TMSCHN_2$ to give methyl ester **27**. Removal of the EE group by treatment with hydrochloric acid in diethyl ether then delivered **18**. Thus, diastereomeric alcohols **24a** and **24b** were convergently used for the synthesis of hydroxy ester **18**.

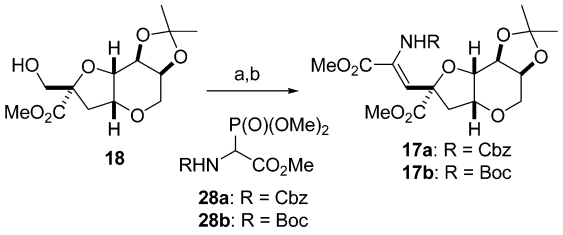
We next converted alcohol **18** to the requisite enamide esters *N*-Cbz-protected **17a** and *N*-Boc-protected **17b** in a two-step procedure (Scheme 6). Oxidation of **18** under Swern conditions

SCHEME 5[a]



[a] Reagents and conditions: (a) ethyl vinyl ether, *p*-TsOH·H_2O, CH_2Cl_2, rt, 97%; (b) TBAF, THF, rt, quantitative; (c) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C; (d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O, rt; (e) $(TMS)CHN_2$, MeOH, rt, 80% (three steps); (f) HCl, Et_2O, 0 °C, 91%.

SCHEME 6[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt; (b) **28a** or **28b**, tetramethylguanidine, CH_2Cl_2, rt, (**17a**) 81% (two steps), (**17b**) 80% (two steps).

followed by HWE olefination using phosphonates **28a** and **28b**[21] and *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) generated enamide esters **17a** and **17b** in 81% and 80% yield for the two steps, respectively.

With the desired enamide esters **17** now available, we were positioned to investigate the asymmetric hydrogenation (Table 2). The reaction was first attempted on the *N*-Cbz-protected **17a** in the presence of 0.5 mol % $[Rh^I(COD)$-(*S*,*S*)-EtDuPHOS$]^+OTf^-$ catalyst[16] in methanol under pressurized hydrogen (0.4 MPa) at room temperature; however, the desired amino acid derivative **29a** was not obtained (entry 1). When the reaction was performed under higher pressure (0.8 MPa) in THF, the desired product **29a** was obtained, albeit in a low yield (22%), with complete stereoselectivity (entry 2). The yield of **29a** was further improved by using 1 mol % catalyst (entry 3). When the reaction was carried out at 40 °C, no improvement of the yield was observed (entry 4). Finally, the best result was obtained by using 5 mol % catalyst to give the desired **29a** in 85% yield and with a diastereomeric ratio of >20:1 (entry 5). The corresponding diastereomer could not be detected in entries 2−5 in the 500 MHz ^1H NMR spectra. The stereochemistry of the product **29a**

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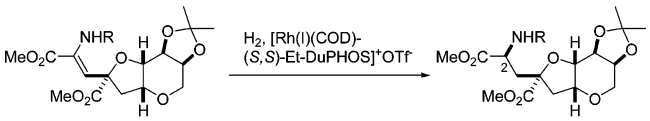
TABLE 2. Asymmetric Hydrogenation of Enamide Ester 17



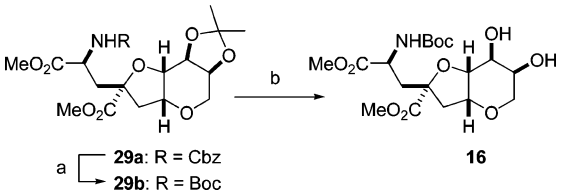
17a: R = Cbz
17b: R = Boc

29a: R = Cbz
29b: R = Boc

entry	enamide ester	catalyst concn (mol %)	H_2 pressure (MPa)	solvent	temp	time (h)	yield (%)	dr (2*S*:2*R*)[a]
1	**17a**	0.5	0.4	MeOH	rt	48	0	−
2	**17a**	0.5	0.8	THF	rt	48	22[b]	>20:1
3	**17a**	1.0	0.8	THF	rt	120	53[c]	>20:1
4	**17a**	1.0	0.8	THF	40 °C	120	55[d]	>20:1
5	**17a**	5.0	0.8	THF	rt	96	85	>20:1
6	**17b**	5.0	0.8	THF	rt	96	90	6:1

[a] Determined by 500 MHz ^{1}H NMR. [b] **17a** was recovered in 70% yield. [c] **17a** was recovered in 32%. [d] **17a** was recovered in 30% yield.

SCHEME 7[a]



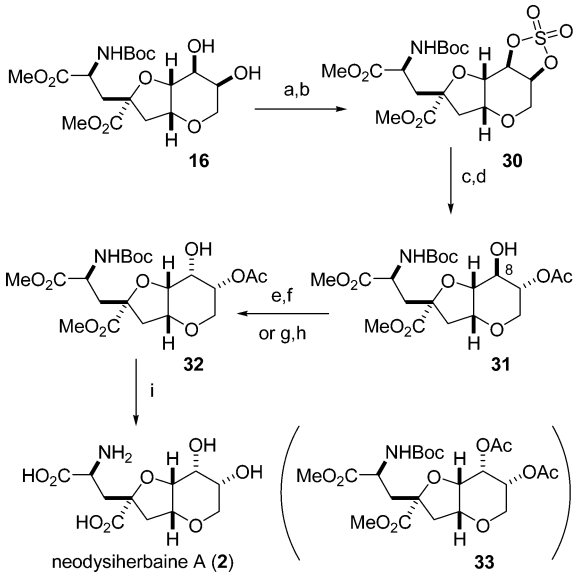
[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$/C, Boc_2O, hexane/MeOH, quantitative; (b) DDQ, CH_3CN/H_2O, 55 °C, 80%.

was tentatively assigned on the basis of Burk's empirical rule,[16] and was confirmed later. In contrast to the case of **17a**, hydrogenation of *N*-Boc-protected enamide ester **17b** under the optimized conditions resulted in a moderate selectivity (dr = 6:1, entry 6). This result is apparently caused by the steric demand of the bulky Boc protective group, which would interfere in the diastereoselective interaction of the olefin moiety with the rhodium catalyst. Hydrogenation of **17b** under achiral conditions (H_2, $Pd(OH)_2$/C, hexane/methanol) produced a 1:1 mixture of diastereomers, providing a comparison for diastereomeric ratio determination.

The Cbz group of **29a** was replaced with the Boc group by hydrogenolysis in the presence of Boc_2O to furnish **29b** in quantitative yield, which was completely identical with that previously synthesized (Scheme 7). After several experiments, selective removal of the acetonide group within **29b** was realized by the action of DDQ ($MeCN/H_2O$, 55 °C),[22] and the desired **16** was obtained in 80% yield without any loss of the Boc group. Thus, the advanced key intermediate **16** was concisely prepared from **9** in 12% overall yield over 16 steps.

Total Synthesis of Neodysiherbaine A. Having established a concise synthetic route to **16**, we next set out to synthesize **2** from this advanced intermediate. Thus, *cis*-diol **16** was converted to cyclic sulfate ester **30** in 91% yield by a two-step sequence, including cyclic sulfite formation with $SOCl_2$ and triethylamine followed by oxidation using $RuCl_3/NaIO_4$ (Scheme 8).[23] Treatment of **30** with cesium acetate (DMF, 65 °C) effected regioselective substitution at the C_9 position to produce acetate

SCHEME 8[a]



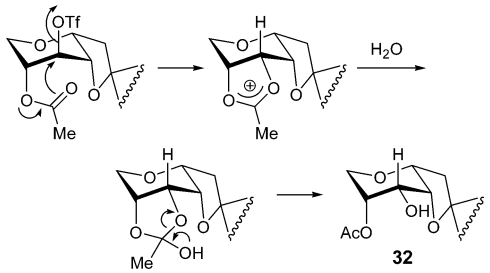
[a] Reagents and conditions: (a) $SOCl_2$, Et_3N, CH_2Cl_2, −20 °C; (b) catalytic $RuCl_3$, $NaIO_4$, $CCl_4/MeCN/H_2O$, rt, 91% (two steps); (c) CsOAc, DMF, 65 °C; (d) catalytic H_2SO_4, THF, rt, 83% (two steps); (e) catalytic TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt; (f) $NaBH_4$, MeOH, −40 °C, 30−77% (two steps); (g) Tf_2O, pyridine, DMAP, CH_2Cl_2, −20 °C; (h) CsOAc, DMF, rt, 71% (two steps); (i) 6 M HCl, 85 °C, 93%.

31 in 83% yield after acid hydrolysis of the resultant sulfate ester. Inversion of the C_8 hydroxy group was next attempted by an oxidation−reduction sequence; however, this protocol lacked reproducibility (30−77% yield). Therefore, we decided to undertake inversion of the C_8 alcohol by nucleophilic substitution. Triflation of **31** using triflic anhydride and pyridine proceeded cleanly to give the corresponding triflate. Subsequent treatment with cesium acetate led to alcohol **32** with the inverted C_8 stereochemistry in 71% yield over the two steps, and the expected diacetate **33** was not obtained at all. Although this transformation can be rationalized by neighboring group participation of the C_9 acetoxy group, we do not have an explanation of why the acetyl group remains at the C_9 position (Scheme 9). In addition, since the use of DMAP instead of cesium acetate also effected this inversion of the C_8 configuration, the role of cesium acetate was just that of an acid scavenger. Finally, acidic hydrolysis of alcohol **32** completed the synthesis of **2** in 93% yield, which was identical to the natural sample.[7]

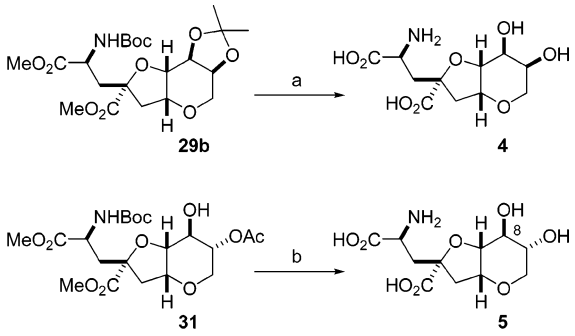
(22) (a) Fernandez, J. M. G.; Mellet, C. O.; Martin, A. M.; Fuentes, J. *Carbohydr. Res.* **1995**, *274*, 263−268. (b) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475−8485. (c) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435−2446.

(23) For a review of cyclic sulfates, see: Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051−7079.

SCHEME 9

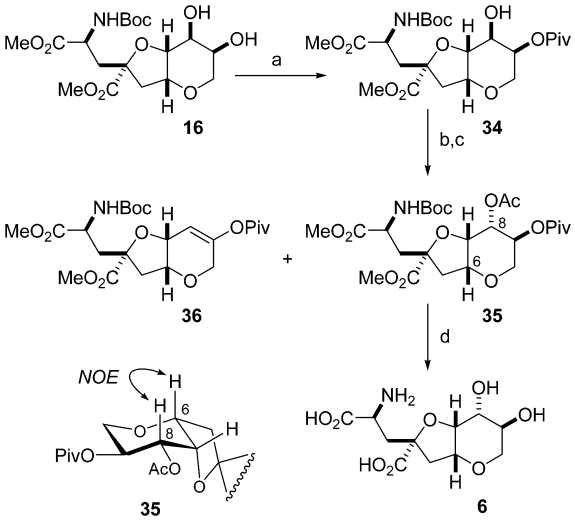


SCHEME 10[a]



[a] Reagents and conditions: (a) 6 M HCl, 65 °C, 94%; (b) 6 M HCl, 85 °C, 90%.

SCHEME 11[a]

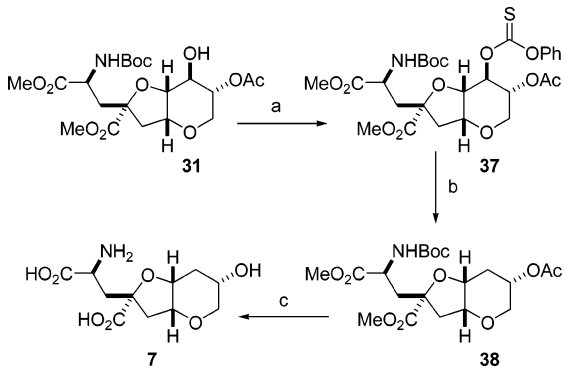


[a] Reagents and conditions: (a) PivCl, Et_3N, DMAP, CH_2Cl_2, −50 °C, 82%; (b) Tf_2O, pyridine, DMAP, CH_2Cl_2, −20 °C; (c) CsOAc, DMF, 50 °C, (**35**) 37% (two steps), (**36**) 11% (two steps); (d) 6 M HCl, 100 °C, quantitative.

Synthesis of Analogues. Analogues **4** and **6** were prepared by acid hydrolysis of intermediates **29b** and **31**, respectively (Scheme 10).

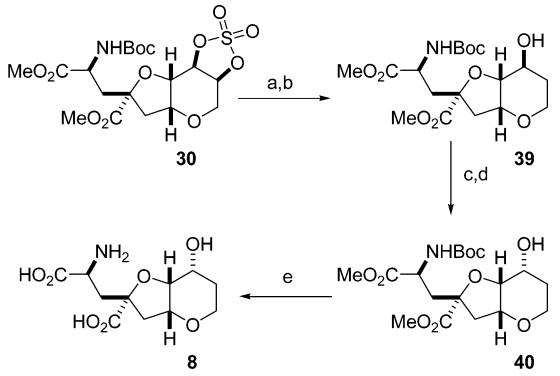
Synthesis of analogue **6** is summarized in Scheme 11. Selective protection of the C_9 hydroxy group of **16** was performed with pivaloyl chloride, triethylamine, and DMAP in CH_2Cl_2 to provide pivalate ester **34** in 82% yield. The remaining C_8 hydroxy group was triflated (triflic anhydride, pyridine), and subsequent nucleophilic substitution by cesium acetate provided acetate **35** in 37% yield over the two steps. In this reaction, elimination product **36** was produced as a significant byproduct. Formation of **36** could not be avoided under various conditions.

SCHEME 12[a]



[a] Reagents and conditions: (a) PhOC(S)Cl, DMAP, toluene, reflux, 73%; (b) *n*-Bu_3SnH, AIBN, toluene, reflux, 78%; (c) 6 M HCl, 85 °C, 92%.

SCHEME 13[a]



[a] Reagents and conditions: (a) $NaBH_4$, DMA, rt; (b) catalytic H_2SO_4, THF, rt, 51% (two steps); (c) catalytic TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt; (d) $NaBH_4$, MeOH, −20 °C, 88% (two steps); (e) 6 M HCl, 65 °C, 90%.

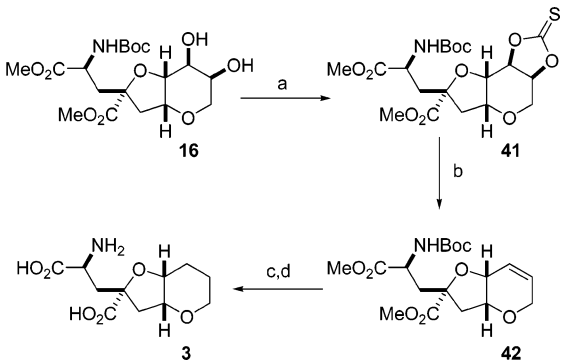
The C_8 stereochemistry of **35** was determined by the observed NOE between 6-H and 8-H as shown. Finally, global deprotection of **35** with 6 M HCl at 100 °C afforded **6** in quantitative yield.

Analogue **7** was prepared as shown in Scheme 12. Alcohol **31** was converted to the corresponding phenyl thiocarbonate **37** by the action of phenyl chlorothionoformate and DMAP in refluxing toluene (73% yield). Subsequent deoxygenation proceeded smoothly under radical conditions (Bu_3SnH, AIBN, toluene, reflux) to deliver **38** in 78% yield. Acidic hydrolysis of **38** generated **7** in 92% yield.

The synthesis of **8** is summarized in Scheme 13. Treatment of **30** with sodium borohydride effected reductive ring opening of the cyclic sulfate to yield, after acid hydrolysis of the resultant sulfate monoester, alcohol **39** in 51% yield over the two steps. The β-oriented hydroxy group of **39** was then inverted by an oxidation−reduction sequence to produce α-alcohol **40** in 88% yield for the two steps. Finally, global deprotection by acid hydrolysis furnished **8** in 90% yield.

Analogue **3**, which was a selective, competitive antagonist for GluR5-containing kainate receptors,[8,9] was also prepared from diol **16** (Scheme 14). Treatment of diol **16** with thiocarbonyldiimidazole and DMAP in refluxing toluene generated cyclic thiocarbonate **41** in 80% yield without epimerization at the C_2 position. Subsequent reductive deoxygenation of the C_8 and C_9 oxygen functionalities was performed by the Corey−Winter method using 1,3-dimethyl-2-phenyl-1,3,2-diazaphos-

SCHEME 14[a]



[a] Reagents and conditions: (a) (imidazole)$_2$C=S, DMAP, toluene, 70 °C, 80%; (b) 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, THF, 40 °C, 73%; (c) H_2, Pd(OH)$_2$/C, hexane/MeOH, rt, 94%; (d) 6 M HCl, 65 °C, 85%.

TABLE 3. Epileptogenic Activity of Natural Dysiherbaines 1 and 2 and Synthetic Analogues 4−8

entry	compd	ED_{50} (nmol/mouse, icv)	entry	compd	ED_{50} (nmol/mouse, icv)
1	DH (**1**)	1.3×10^{-2}	5	**6**	9.4
2	NDH (**2**)	1.6×10^{-2}	6	**7**	0.17
3	**4**	no activity[a]	7	**8**	6.7
4	**5**	0.23			

[a] Did not induce convulsant behaviors at 69 nmol/mouse.

pholidine[24] to give olefin **42** in 73% yield. Finally, hydrogenation of the double bond followed by acid hydrolysis furnished analogue **3** in 80% yield for the two steps. According to the newly developed procedures, analogue **3** was prepared even on a 100 mg scale with good reproducibility.

Biological Evaluation of Dysiherbaine Analogues. The in vivo toxicity of analogues **4**−**8** against mice was determined by intracerebroventricular injection. Among the analogues tested, 9-*epi*, 8-deoxy, and 9-deoxy analogues (**6**, **7**, and **8**, respectively) elicited behavior in a dose-dependent manner. The seizure behavior observed after injection of these analogues corresponded well to that observed in **1**, with the exception that such behavior seldom recurred. The ED_{50} values for analogues **6**, **7**, and **8** were 9.4, 0.17, and 6.7 nmol/mouse, respectively (Table 3). 8,9-*epi* analogue **4** did not induce noticeable convulsant behavior even at a higher dose (69 nmol/mouse), although mice became relatively hypoactive for a while. Injection of **5** also resulted in the induction of seizures with an ED_{50} value of 0.23 nmol/mouse. Interestingly, the behavioral profile of **5** was substantially different from that of **1**. Stereotyped behaviors, such as persistent scratching or clonic convulsions, frequently observed after administration of **1**, were absent in the case of **5**. Instead, transient jumping and running behaviors were apparent.

The binding affinities of analogues **4**−**8** were first evaluated with native ionotropic glutamate receptors by radioligand binding assays using rat synaptic membrane preparation (Table 4).[5] Analogues **5**−**8**, which possess a hydroxy group with at least the same configuration as that of the natural product on the C_8 and/or C_9 position, showed affinities for AMPA and kainate receptors, whereas analogue **4** had no significant affinity. These results were consistent with the behavioral activity described above. Among active analogues with binding affinities, 8-deoxy analogue **7** showed the highest affinity for both AMPA and kainate receptors, but was 20-fold less potent than the natural product **2**. Interestingly, **5** and **6** displaced [^{3}H]-AMPA more potently than [^{3}H]kainic acid from the receptors. None of the analogues exhibited a detectable affinity for NMDA receptors.

TABLE 4. Receptor Binding Affinities of Natural Dysiherbaines 1 and 2 and Synthetic Analogues 4−8 for Native AMPA and Kainate Receptors[a]

entry	compd	[^{3}H]AMPA	[^{3}H]kainic acid
1[b]	DH (**1**)	0.153 ± 0.01110	0.026 ± 0.004
2[c]	NDH (**2**)	0.227 ± 0.0405	0.066 ± 0.005
3	**4**	>100	>100
4	**5**	9.7 ± 2.3	24.1 ± 6.8
5	**6**	32 ± 11	91 ± 35
6	**7**	4.2 ± 1.6	1.4 ± 0.35
7	**8**	68.1 ± 17.9	31.8 ± 14.1

[a] Affinities for receptors (IC_{50}, μM) were determined by the displacement of [^{3}H]AMPA and [^{3}H]kainic acid from rat synaptic membrane preparations. [b] K_i values (μM), reference 5. [c] K_i values (μM), reference 9.

TABLE 5. Receptor Binding Affinities of Natural Dysiherbaines 1 and 2 and Synthetic Analogues 4, 5, 7, and 8 for Recombinant Kainate Receptors[a,b]

entry	compd	GluR5	GluR6	KA2
1	DH (**1**)	0.48[c]	1.28[c]	4300[d]
2	NDH (**2**)	7.7[e]	33[e]	600[e]
3	**4**	48000	>100000	>100000
4	**5**	34	22000	>100000
5	**7**	1.1	42	36000
6	**8**	168	>100000	>100000

[a] Affinities for receptors (K_i, nM) were determined by the radioligand binding assays using HEK 293 cells expressing the appropriate KA receptor subunits. [b] [^{3}H]Kainic acid was used as a radioligand. [c] Reference 5. [d] Reference 6. [e] Reference 9.

To estimate the binding affinities of analogues **4**, **5**, **7**, and **8** to the kainate receptor subunits, the radioligand binding assay was next performed using recombinant homomeric kainate receptor subunits (GluR5, GluR6, and KA2 receptors) expressed in HEK 293 cells. The results are summarized in Table 5. Although **4** did not bind detectably to native kainate receptors, it displaced [^{3}H]kainic acid from homomeric GluR5 kainate receptors. The binding affinity of analogues **4**, **5**, **7**, and **8** for GluR5 kainate receptors correlated well with their epileptogenic potency in mice, suggesting that activation of the GluR5 kainate receptor subunit directly results in seizure behaviors. In contrast, the affinity for the GluR6 or KA2 subunits poorly correlates with the epileptogenic potency. Especially, the potently convulsant 8-deoxy analogue **7** exhibited a high affinity for GluR5 receptors comparable to that of the natural product **2**, but its affinity for GluR6 receptors was greatly reduced. These results suggest that the α-oriented C_9 hydroxy group is a critical structural element required for highly selective binding to the GluR5 kainate receptors.

Conclusion. We have developed an efficient synthetic route to **2** and its analogues **3**−**8**, which features (i) a concise synthesis of the bicyclic ether skeleton through stereoselective *C*-glycosylation to set the C_6 stereocenter and 5-*exo* cyclization for constructing the tetrahydrofuran ring and (ii) stereoselective construction of the amino acid appendage through catalytic asymmetric hydrogenation of enamide ester. The preliminary

(24) (a) Corey, E. J.; Winter, A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677−2678. (b) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979−1982.

structure−activity relationship studies described herein revealed that the α-oriented C_9 hydroxy group is a critical element required for selective binding to the GluR5 kainate receptor subunit. More detailed neurophysiological studies of analogues **4**−**8** and newer analogues will not only facilitate an in-depth understanding of the structure−function relationship between dysiherbaine analogues and glutamate receptors but also lead us to the development of compounds with therapeutic utility. Further investigations along these lines are currently under way and will be reported in due course.

Experimental Section

***C*-Glycoside 11.** To a solution of 3,4-di-*O*-acetyl-L-arabinal (**9**; 11.92 g, 59.6 mmol) and allylsilane **10** (16.8 g, 71.5 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added $Yb(OTf)_3$ (5.54 g, 8.94 mmol). The reaction mixture was stirred at room temperature for 2.5 h and treated with water (50 mL). The mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (150 g, triethylamine:ethyl acetate:hexanes = 0.1:1:10) afforded *C*-glycoside **11** (15.7 g, 87%) as a colorless oil: $[\alpha]_D^{26}$ −110.1 (*c* 0.25, $CHCl_3$); IR (film) 2927, 2857, 2359, 2342, 1734, 1370, 1236, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5 H), 5.92 (d, *J* = 10.0 Hz, 1 H), 5.82 (d, *J* = 10.0 Hz, 1 H), 5.19 (s, 1 H), 5.16 (s, 1 H), 5.03 (s, 1 H), 4.48 (s, 2 H), 4.31 (s, 1 H), 4.07 (dd, *J* = 12.0, 5.0 Hz, 1 H), 4.02 (d, *J* = 16.0 Hz, 1 H), 3.99 (d, *J* = 16.0 Hz, 1 H), 3.53 (dd, *J* = 12.0, 6.0 Hz, 1 H), 2.37 (dd, *J* = 14.5, 8.0 Hz, 1 H), 2.29 (dd, *J* = 14.5, 5.0 Hz, 1 H), 2.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 142.1, 138.2, 128.4 (×2), 127.8, 127.6, 124.0, 123.9, 115.0, 73.0, 72.0, 71.8, 64.9, 64.8, 64.7, 37.6, 21.2; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{23}O_4$ [(M + H)$^+$] 303.1596, found 303.1604.

Diol 19. To a solution of OsO_4 (1% solution in *tert*-butyl alcohol, 19.0 mL, 0.750 mmol), $(DHQD)_2AQN$ (1.29 g, 1.50 mmol), K_2CO_3 (6.22 g, 45.0 mmol), and $K_2[Fe(CN)_6]$ (14.8 g, 45.0 mmol) in water (40 mL) at 0 °C were successively added diene **11** (4.53 g, 15.0 mmol) in *tert*-butyl alcohol (40 mL) and methanesulfonamide (4.28 g, 45.0 mmol). The reaction mixture was stirred for 3 h and then quenched with saturated aqueous Na_2SO_3 (40 mL). The resulting mixture was stirred at room temperature for an additional 30 min. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 300 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (150 g, ethyl acetate: hexanes = 1:1) afforded diol **19** (4.07 g, 80%, an inseparable 3:1 mixture of diastereomers) as a colorless oil: $[\alpha]_D^{26}$ −67.0 (*c* 1.03, $CHCl_3$); IR (film) 3446, 2925, 2359, 1733, 1418 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.35−7.26 (m, 5 H), 5.82−5.79 (m, 2 H), 5.21 (dd, *J* = 4.0, 2.0 Hz, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.49 (d, *J* = 11.5 Hz, 1 H), 4.46−4.43 (m, 1 H), 4.09 (d, *J* = 5.5 Hz, 1 H), 3.55 (d, *J* = 6.5 Hz, 2 H), 3.51 (dd, *J* = 11.0, 6.5 Hz, 1 H), 3.49 (d, *J* = 9.0 Hz, 1 H), 3.46 (s, 1H), 3.45 (d, *J* = 12.0 Hz, 1 H), 3.41 (d, *J* = 9.0 Hz, 1 H), 2.62 (t, *J* = 14.0 Hz, 1 H), 2.06 (s, 3 H), 1.76−1.74 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer) δ 170.5, 137.8, 134.0, 128.4, 127.8 (×2), 127.7 (×2), 124.1, 73.4, 73.2, 70.5, 66.8, 64.6, 60.3, 37.1, 20.9, 14.1; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{25}O_6$ [(M + H)$^+$] 337.1651, found 337.1654.

TBDMS Ether 20. To a solution of diol **19** (9.21 g, 27.6 mmol), triethylamine (9.30 mL, 66.2 mmol), and DMAP (674 mg, 5.52 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added TBDMSOTf (6.90 mL, 30.3 mmol). The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with ethyl acetate (500 mL) and washed successively with water (80 mL), aqueous 1 M HCl (80 mL), saturated aqueous $NaHCO_3$ (80 mL), and brine (80 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (100 g, ethyl acetate:hexanes = 1:4) afforded TBDMS ether **20** (10.6 g, 85%, an inseparable 3:1 mixture of diastereomers) as a colorless oil: $[\alpha]_D^{26}$ −66.2 (*c* 0.72, $CHCl_3$); IR (film) 3522, 2928, 2856, 1736, 1237, 1094, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.35−7.25 (m, 5 H), 5.88 (d, *J* = 10.0 Hz, 1 H), 5.81 (dt, *J* = 10.5, 2.5 Hz, 1 H), 5.15 (d, *J* = 3.0 Hz, 1 H), 4.55 (d, *J* = 9.0 Hz, 1 H), 4.53 (dd, *J* = 10.0, 2.5 Hz, 1 H), 4.51 (d, *J* = 9.0 Hz, 1 H), 4.04 (dd, *J* = 12.0, 3.5 Hz, 1 H), 3.57 (dd, *J* = 4.0, 2.0 Hz, 1 H), 3.55−3.54 (m, 2 H), 3.45−3.44 (m, 2 H), 3.12 (s, 1H), 2.06 (s, 3 H), 1.85 (dd, *J* = 14.5, 5.0 Hz, 1 H), 1.62 (dd, *J* = 14.5, 2.5 Hz, 1 H), 0.85 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer) δ 169.1, 135.6 (×2), 128.6, 127.9 (×2), 126.5 (×2), 123.3, 78.9, 73.7, 73.2, 70.4, 66.2, 65.0, 64.3, 36.9, 25.9 (×3), 21.3, 18.2, −4.5 (×2); HRMS (FAB) *m*/*z* calcd for $C_{24}H_{39}O_6Si$ [(M + H)$^+$] 451.2516, found 451.2520.

Acetonide 23. To a solution of TBDMS ether **20** (11.5 g, 25.5 mmol) in methanol (150 mL) at room temperature was added K_2CO_3 (702 mg, 5.00 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated under reduced pressure to give an oily solid. The residue was purified by flash column chromatography on silica gel (100 g, ethyl acetate:hexanes = 1:1) to afford allylic alcohol (9.73 g, 95%, an inseparable 3:1 mixture of diastereomers) as a colorless oil: $[\alpha]_D^{26}$ −58.6 (*c* 0.72, $CHCl_3$); IR (film) 3410, 2927, 2359, 2341 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.33−7.25 (m, 5 H), 5.86 (dt, *J* = 10.0, 3.0 Hz, 1 H), 5.74 (d, *J* = 10.0 Hz, 1 H), 4.55 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.46 (d, *J* = 10.0 Hz, 1 H), 4.10 (m, 1 H), 3.99 (dd, *J* = 11.5, 4.0 Hz, 1 H), 3.56 (s, 2 H), 3.45 (s, 2 H), 3.44 (dd, *J* = 11.0, 5.5 Hz, 1 H), 3.25 (s, 1H), 1.82 (dd, *J* = 14.5, 5.0 Hz, 1 H), 1.67 (d, *J* = 8.5 Hz, 1H), 1.63 (dd, *J* = 15.0, 6.0 Hz, 1 H), 0.84 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer) δ 138.2, 133.3, 128.3 (×2), 127.6 (×2), 127.5, 127.4, 73.6, 73.4, 72.8, 70.4, 67.6, 66.2, 62.6, 36.4, 25.8 (×3), 18.2, −5.5 (×2); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{37}O_5Si$ [(M+H)$^+$] 409.2410, found 409.2416.

To a solution of allylic alcohol (8.70 g, 21.3 mmol) in CH_2Cl_2 and pH 7 phosphate buffer (9:1, v/v, 150 mL) at 0 °C was added *m*-CPBA (65%, 8.5 g, 32 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with saturated aqueous Na_2SO_3 (100 mL), and then stirred for an additional 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (100 g, ethyl acetate:hexanes = 1:1) afforded diol **22** (8.10 g, 89%, an inseparable 3:1 mixture of diastereomers) as a colorless oil.

To a solution of the above diol **22** (8.09 g, 19.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C were added CSA (882 mg, 3.80 mmol) and 2,2-dimethoxypropane (23 mL, 190 mmol). The reaction mixture was stirred at 0 °C for 2 h and then quenched with triethylamine (5 mL). The solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (100 g, ethyl acetate:hexanes = 1:9) to afford acetonide **23** (7.50 g, 85%, an inseparable 3:1 mixture of diastereomers) as a colorless oil: $[\alpha]_D^{26}$ −5.5 (*c* 0.66, $CHCl_3$); IR (film) 2928, 2857, 2359, 2342, 1085, 1062 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.34−7.25 (m, 5H), 4.53 (d, *J* = 13.0 Hz, 1 H), 4.50 (d, *J* = 13.0 Hz, 1 H), 4.42 (s, 1 H), 4.19 (dt, *J* = 11.0, 7.0 Hz, 1 H), 4.16 (s, 1 H), 4.07 (dd, *J* = 12.0, 2.5 Hz, 1 H), 3.73 (q, *J* = 6.0 Hz, 1 H), 3.65 (d, *J* = 9.0 Hz, 1 H), 3.61 (d, *J* = 11.0 Hz, 1 H), 3.52 (d, *J* = 15.0 Hz, 1 H), 3.45 (d, *J* = 15.0 Hz, 1 H), 3.10 (t, *J* = 11.0 Hz, 1 H), 2.23 (dd, *J* = 14.5, 5.5 Hz, 1 H), 1.99 (d, *J* = 14.5 Hz, 1 H), 1.44 (s, 6 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer) δ 138.0, 128.2, 127.5 (×2), 127.4 (×2), 108.4, 84.1, 78.1, 76.2, 73.5, 73.3,

72.9, 72.4, 68.9, 65.7, 65.5, 37.0, 27.9, 25.8 (×3), 18.2, −5.4 (×2); HRMS (FAB) *m/z* calcd for $C_{25}H_{41}O_6Si$ [(M + H)$^+$] 465.2672, found 465.2672.

Alcohols 24a and 24b. A suspension of acetonide **23** (3.77 g, 8.12 mmol) and 10% Pd/C (377 mg) in hexane (80 mL) at room temperature was stirred under a hydrogen atmosphere for 2 h. The reaction mixture was filtered through a short pad of Celite, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (100 g, ethyl acetate:hexanes = 1:9) afforded (4*R*)-alcohol **24a** (2.27 g, 75%) and its diastereomeric (4*S*)-alcohol **24b** (609 mg, 20%) as colorless oils. Data for (4*R*)-alcohol **24a**: $[\alpha]_D^{26}$ −21.8 (*c* 0.18, $CHCl_3$); IR (film) 3481, 2952, 2359, 1085, 1062, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (d, *J* = 5.5 Hz, 1 H), 4.20 (dt, *J* = 11.0, 5.5 Hz, 1 H), 4.09 (s, 1 H), 4.07 (dd, *J* = 5.0, 2.5 Hz, 1 H), 3.77 (q, *J* = 6.0 Hz, 1 H), 3.69 (d, *J* = 9.5 Hz, 1 H), 3.62 (dd, *J* = 12.0, 7.0 Hz, 1 H), 3.59 (d, *J* = 9.5 Hz, 1 H), 3.56 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.10 (t, *J* = 11.0 Hz, 1 H), 2.25 (t, *J* = 6.5 Hz, 1 H), 2.07 (d, *J* = 15.0 Hz, 1 H), 1.99 (dd, *J* = 15.0, 5.0 Hz, 1 H), 1.44 (s, 3 H), 1.33 (s, 3 H), 0.86 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.9, 85.0, 78.2, 76.5, 72.4, 68.8, 66.3, 66.1, 65.9, 36.7, 28.3, 26.5, 26.0 (×3), 18.4, −5.2, −5.3; HRMS (FAB) *m/z* calcd for $C_{18}H_{35}O_6Si$ [(M + H)$^+$] 375.2203, found 375.2209. Data for (4*S*)-alcohol **24b**: $[\alpha]_D^{26}$ −12.1 (*c* 0.56, $CHCl_3$); IR (film) 3481, 2929, 2359, 1085, 1063, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.40 (d, *J* = 5.5 Hz, 1 H), 4.24 (dt, *J* = 11.0, 5.5 Hz, 1 H), 4.11 (s, 1 H), 4.07 (dd, *J* = 5.0, 2.0 Hz, 1 H), 3.80 (q, *J* = 6.0 Hz, 1 H), 3.55 (d, *J* = 6.0 Hz, 2 H), 3.54 (s, 2 H), 3.14 (t, *J* = 11.0 Hz, 1 H), 2.61 (t, *J* = 5.3 Hz, 1 H), 2.23 (dd, *J* = 14.0, 5.3 Hz, 1 H), 1.98 (d, *J* = 14.0 Hz, 1 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 0.87 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.6, 83.8, 77.7, 76.2, 72.4, 68.9, 66.9, 66.4, 65.7, 37.2, 28.0 (×2), 25.9, 25.8 (×2), 18.1, −5.5 (×2); HRMS (FAB) *m/z* calcd for $C_{18}H_{35}O_6Si$ [(M + H)$^+$] 375.2203, found 375.2207.

Methyl Ester 25. To a solution of alcohol **24a** (3.26 g, 9.40 mmol) in CH_2Cl_2/DMSO (4:1, v/v, 80 mL) at 0 °C were successively added triethylamine (6.50 mL, 47.0 mmol) and SO_3·pyridine (5.98 g, 37.6 mmol). The resultant mixture was stirred at room temperature for 1.5 h. The mixture was then extracted with ethyl acetate (3 × 200 mL), and the combined organic layers were successively washed with aqueous 1 M HCl (80 mL), saturated aqueous $NaHCO_3$ (80 mL), and brine (80 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude aldehyde as a colorless oil.

To a solution of the above aldehyde in *tert*-butyl alcohol/water (5:1, v/v, 70 mL) at 0 °C were added 2-methyl-2-butene (17.0 mL), NaH_2PO_4 (1.24 g, 10.3 mmol), and $NaClO_2$ (2.81 g, 31.0 mmol). The resultant mixture was stirred at room temperature for 2 h and then poured into $CHCl_3$/water (3:1, v/v, 200 mL). The mixture was acidified to pH 2 with aqueous 1 M HCl. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (5 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude carboxylic acid as a colorless oil.

To a solution of the above carboxylic acid in methanol/benzene (1:1, v/v, 80 mL) at room temperature was added $TMSCHN_2$ (2 M in Et_2O, 14.0 mL, 28 mmol). The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. Purification by flash column chromatography on silica gel (200 g, ethyl acetate:hexanes = 1:4) afforded methyl ester **25** (10.6 g, 85% for the three steps) as a colorless oil: $[\alpha]_D^{26}$ −11.0 (*c* 0.44, $CHCl_3$); IR (film) 2953, 2929, 2362, 1733, 1249, 1086, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (d, *J* = 5.5 Hz, 1 H), 4.24 (dt, *J* = 10.5, 5.5 Hz, 1 H), 4.19 (s, 1 H), 4.06 (s, 1 H), 3.82 (d, *J* = 11.0 Hz, 1 H), 3.71 (dd, *J* = 13.0, 6.5 Hz, 1 H), 3.70 (s, 3 H), 3.67 (d, *J* = 10.0 Hz, 1 H), 3.08 (t, *J* = 10.5 Hz, 1 H), 2.45 (d, *J* = 14.0 Hz, 1 H), 2.31 (dd, *J* = 14.0, 4.5 Hz, 1 H), 1.44 (s, 3 H), 1.35 (s, 3 H), 0.85 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 108.3, 86.4, 78.9, 74.8, 72.3, 68.2, 66.4, 64.9, 51.9, 51.8, 38.5, 27.8, 25.7, 25.6 (×3), −5.7, −5.6; HRMS (FAB) *m/z* calcd for $C_{19}H_{35}O_7Si$ [(M + H)$^+$] 403.2152, found 403.2156.

Alcohol 18. To a solution of TBDMS ether **25** (528 mg, 1.30 mmol) in THF (9.0 mL) at room temperature was added TBAF (1.0 M in THF, 4.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure. Purification by flash column chromatography on silica gel (20 g, ethyl acetate:hexanes = 3:7) afforded alcohol **18** (313 mg, 85%) as a pale yellow oil: $[\alpha]_D^{26}$ −20.4 (*c* 0.67, $CHCl_3$); IR (film) 3479, 2985, 1732, 1218, 1086, 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (d, *J* = 5.5 Hz, 1 H), 4.25 (dt, *J* = 10.5, 6.0 Hz, 1 H), 4.23 (s, 1 H), 4.09 (s, 1 H), 3.82 (dd, *J* = 12.0, 7.0 Hz, 1 H), 3.73 (s, 3 H), 3.72 (dd, *J* = 18.0, 6.0 Hz, 1 H), 3.63 (dd, *J* = 12.0, 6.5 Hz, 1 H), 3.07 (t, *J* = 10.5 Hz, 1 H), 2.49 (d, *J* = 14.0 Hz, 1 H), 2.23 (dd, *J* = 7.0, 5.5 Hz, 1 H), 1.44 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 108.8, 86.5, 79.3, 75.0, 72.7, 68.7, 66.3, 65.3, 52.5, 39.4, 28.2, 26.1; HRMS (FAB) *m/z* calcd for $C_{13}H_{21}NO_7$ [(M + H)$^+$] 289.1287, found 289.1288.

Cbz-Protected Enamide Ester 17a. To a solution of DMSO (4.05 mL, 57.2 mmol) in CH_2Cl_2 at −78 °C was added oxalyl chloride (3.81 mL, 42.9 mmol). The resultant mixture was stirred at −78 °C for 15 min, and then a solution of alcohol **18** (4.11 g, 14.3 mmol) in CH_2Cl_2 (140 mL) was introduced via cannula. The reaction mixture was stirred at the same temperature for 45 min and then treated with triethylamine (11.9 mL, 85.8 mmol). The resultant mixture was allowed to warm to room temperature over 1 h and quenched with saturated aqueous NH_4Cl (100 mL). The mixture was extracted with ethyl acetate (3 × 250 mL), and the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude aldehyde as a yellow solid.

To a stirred solution of the above aldehyde in CH_2Cl_2 (140 mL) at 0 °C were added $(MeO)_2P(O)CH(NHCbz)CO_2Me$ (**28a**; 14.17 g, 42.90 mmol) and *N*,*N*,*N*′,*N*′-tetramethylguanidine (7.20 mL, 57.2 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl (40 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (300 g, ethyl actetate:hexanes = 3:7) afforded enamide ester **17a** (5.65 g, 81% for the two steps) as a colorless solid: $[\alpha]_D^{26}$ −8.0 (*c* 0.61, $CHCl_3$); IR (film) 3365, 2986, 2952, 2359, 2341, 1733, 1653, 1219, 1062 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (br s, 1 H), 7.35−7.29 (m, 5 H), 6.02 (s, 1 H), 5.14 (s, 2 H), 4.50 (d, *J* = 5.5 Hz, 1 H), 4.26 (s, 1 H), 4.19 (dt, *J* = 10.5, 5.5 Hz, 1 H), 4.05 (s, 1 H), 3.72 (m, 1 H), 3.69 (s, 6 H), 3.04 (t, *J* = 11.0 Hz, 1 H), 2.92 (d, *J* = 13.5 Hz, 1 H), 2.23 (dd, *J* = 13.5, 4.0 Hz, 1 H), 1.43 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 164.3, 153.4, 135.6, 130.5, 128.4 (×2), 128.1 (×2), 128.0, 108.6, 83.8, 78.9, 74.2, 72.3, 68.3, 67.4, 65.9, 60.2, 52.9, 52.5, 43.9, 27.9, 25.9; HRMS (FAB) *m/z* calcd for $C_{24}H_{30}NO_{10}$ [(M + H)$^+$] 492.1870, found 492.1867.

Boc-Protected Enamide Ester 17b. To a solution of DMSO (0.28 mL, 3.0 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C was added oxalyl chloride (0.26 mL, 4.0 mmol). The resultant mixture was stirred at −78 °C for 15 min, and then a solution of alcohol **18** (288 mg, 1.00 mmol) in CH_2Cl_2 (8.0 mL) was introduced via cannula. The reaction mixture was stirred at the same temperature for 45 min and then treated with triethylamine (0.86 mL, 6.00 mmol). The mixture was allowed to warm to room temperature over 1 h and then quenched with saturated aqueous NH_4Cl (10 mL). The reaction mixture was extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude aldehyde as a yellow solid.

To a stirred solution of the above aldehyde in CH_2Cl_2 (10 mL) at 0 °C were added $(MeO)_2P(O)CH(NHBoc)CO_2Me$ (**28b**; 892 mg,

3.00 mmol) and *N*,*N*,*N*′,*N*′-tetramethylguanidine (0.52 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with ethyl acetate (3 × 30 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (15 g, CH_2Cl_2:ethyl acetate:hexanes = 1:2:7) afforded enamide ester **17b** (365 mg, 80% for the two steps) as a pale yellow foam: $[\alpha]_D^{19}$ +2.9 (*c* 0.48, $CHCl_3$); IR (film) 3391, 2982, 1728, 1655, 1459, 1245, 1162, 1084, 1063, 858 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (br s, 1 H), 5.83 (s, 1 H), 4.42 (d, *J* = 7.0 Hz, 1 H), 4.17 (s, 1 H), 4.11 (dt, *J* = 10.0, 6.0 Hz, 1 H), 3.99 (s, 1 H), 3.66 (s, 3 H), 3.62 (s, 3 H), 3.60 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.96 (t, *J* = 11.0 Hz, 1 H), 2.84 (d, *J* = 14.5 Hz, 1 H), 2.17 (dd, *J* = 14.5, 3.5 Hz, 1 H), 1.34 (s, 3 H), 1.34 (s, 9 H), 1.27 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 163.2, 152.9, 131.1, 123.6, 109.4, 84.2, 81.4, 79.9, 74.7, 72.7, 68.7, 65.5, 53.2, 52.7, 44.2, 28.4 (×3), 28.3, 26.2; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{32}NO_{10}$ [(M + H)$^+$] 458.2026, found 458.2029.

Cbz-Protected Amino Acid Derivative 29a. A degassed mixture of [Rh^I(COD)-(*S*,*S*)-EtDuPHOS]OTf (41.0 mg, 0.060 mmol) and enamide ester **17a** (564 mg, 1.14 mmol) in freshly distilled THF (6.0 mL) was placed in a hydrogenation bottle and pressurized with hydrogen to an initial pressure of 0.8 MPa. The reaction mixture was stirred at room temperature for 96 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10 g, CH_2Cl_2:ethyl acetate:hexanes = 1:2:7) to afford Cbz-protected glutamic acid derivative **29a** (486 mg, 85%) as a white solid: $[\alpha]_D^{26}$ +8.4 (*c* 0.67, $CHCl_3$); IR (film) 3348, 2986, 2952, 2359, 2341, 1729, 1244, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5 H), 5.64 (d, *J* = 7.0 Hz, 1 H), 5.11 (d, *J* = 12.5 Hz, 1 H), 5.07 (d, *J* = 12.5 Hz, 1 H), 4.42 (d, *J* = 5.0 Hz, 1 H), 4.34 (dd, *J* = 7.5, 5.5 Hz, 1 H), 4.20 (dt, *J* = 10.5, 5.5 Hz, 1 H), 4.15 (s, 1 H), 4.03 (s, 1 H), 3.73 (s, 3 H), 3.68 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.59 (s, 3 H), 3.03 (t, *J* = 10.5 Hz, 1 H), 2.59 (d, *J* = 14.0 Hz, 1 H), 2.58 (dd, *J* = 14.0, 6.5 Hz, 1 H), 2.18 (dd, *J* = 14.5, 6.5 Hz, 1 H), 2.11 (dd, *J* = 14.5, 4.0 Hz, 1 H), 1.42 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 172.1, 155.8, 136.4, 128.6 (×2), 128.3, (×2), 128.2, 108.8, 83.6, 78.9, 77.5, 72.8, 68.7, 67.0, 65.2, 52.6, 52.4, 51.6, 44.9, 39.6, 28.2, 26.1; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{32}NO_{10}$ [(M + H)$^+$] 494.2026, found 494.2026.

Boc-Protected Amino Acid Derivative 29b. To a solution of **29a** (486 mg, 0.97 mmol) in hexane/methanol (3:2, v/v, 10 mL) at room temperature were added Boc_2O (0.89 mL, 3.80 mmol) and 10% $Pd(OH)_2$/C (50.0 mg). The mixture was stirred at room temperature under a hydrogen atmosphere for 2 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (20 g, ethyl acetate:hexanes = 1:1) to afford **29b** (458 mg, 100%) as a colorless solid: $[\alpha]_D^{19}$ +19.2 (*c* 0.29, $CHCl_3$); IR (film) 3365, 2981, 2952, 2359, 2342, 1749, 1717, 1246, 1164, 1062 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.33 (d, *J* = 7.0 Hz, 1 H), 4.43 (d, *J* = 4.5 Hz, 1 H), 4.30 (dd, *J* = 7.5, 5.5 Hz, 1 H), 4.24 (dt, *J* = 6.5, 4.5 Hz, 1 H), 4.16 (s, 1 H), 4.04 (s, 1 H), 3.72 (dd, *J* = 13.0, 6.5 Hz, 1 H), 3.70 (s, 3 H), 3.69 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.03 (t, *J* = 11.0 Hz, 1 H), 2.59 (d, *J* = 14.5 Hz, 1 H), 2.55 (dd, *J* = 15.0, 5.0 Hz, 1 H), 2.17 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.14 (dd, *J* = 12.0, 4.5 Hz, 1 H), 1.42 (s, 3 H), 1.41 (s, 9 H), 1.39 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 172.1, 154.8, 108.3, 83.2, 79.6, 78.5, 74.4, 72.4, 68.3, 64.8, 60.1, 52.1, 50.6, 44.3, 39.4, 28.3 (×3), 27.8, 25.7; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{34}NO_{10}$ [(M + H)$^+$] 460.2183, found 460.2188.

Advanced Key Intermediate 16. A solution of **29b** (225 mg, 0.49 mmol) and DDQ (22 mg, 0.098 mmol) in CH_3CN/H_2O (9:1, v/v, 5.0 mL) was stirred at 55 °C for 12 h. The mixture was cooled to room temperature and then concentrated under reduced pressure. Purification by flash column chromatography on silica gel (30 g, methanol:$CHCl_3$ = 3:97) afforded diol **16** (163 mg, 80%) as a white solid: $[\alpha]_D^{19}$ +24.5 (*c* 0.28, $CHCl_3$); IR (film) 3435, 2977, 2953, 1734, 1716, 1506, 1164, 1082 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (d, *J* = 7.0 Hz, 1 H), 4.23 (dd, *J* = 7.5, 5.0 Hz, 1 H), 4.16 (s, 1 H), 4.15 (br s, 2 H), 4.01 (s, 1 H), 3.72 (s, 3 H), 3.70 (s, 3 H), 3.52 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.44 (t, *J* = 10.5 Hz, 1 H), 2.95 (br s, 1 H), 2.61 (d, *J* = 14.0 Hz, 1 H), 2.59 (dd, *J* = 7.0, 5.5 Hz, 1 H), 2.16 (dd, *J* = 14.0, 5.5 Hz, 1 H), 2.06 (dd, *J* = 13.0, 3.5 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 172.2, 154.8, 83.3, 82.4, 79.7, 72.7, 66.4, 63.8, 63.5, 52.3, 52.1, 50.2, 43.7, 39.7, 27.9 (×3); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{30}NO_{10}$ [(M + H)$^+$] 420.1870, found 420.1869.

Cyclic Sulfate 30. To a solution of diol **16** (254 mg, 0.61 mmol) in CH_2Cl_2 (7.0 mL) at −20 °C were added triethylamine (0.23 mL, 1.71 mmol) and thionyl chloride (0.100 mL, 1.46 mmol). The resultant mixture was stirred at −20 °C for 30 min and then poured into ice−water (5 mL). The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a cyclic sulfite (265 mg) as a white solid.

To a solution of the above cyclic sulfite in CH_3CN/CCl_4 (4:5, v/v, 9.0 mL) at room temperature were added $NaIO_4$ (487 mg, 2.28 mmol) and $RuCl_3$ (24 mg, 0.11 mmol) followed by water (4.0 mL). The resultant mixture was stirred at room temperature for 1 h and then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10 g, ethyl acetate:hexanes = 3:7) afforded cyclic sulfate **30** (245 mg, 91% for the two steps) as a white solid: $[\alpha]_D^{26}$ +66.8 (*c* 0.11, $CHCl_3$); IR (film) 3421, 2954, 2359, 1746, 1714, 1392, 1213, 985 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, *J* = 4.5 Hz, 1 H), 5.21 (d, *J* = 7.5 Hz, 1 H), 5.02 (dt, *J* = 11.0, 5.5 Hz, 1 H), 4.32 (s, 1 H), 4.33 (dd, *J* = 7.5, 5.0 Hz, 1 H), 4.19 (t, *J* = 3.5 Hz, 1 H), 3.97 (dd, *J* = 12.0, 6.5 Hz, 1H), 3.69 (s, 3 H), 3.67 (s, 3 H), 3.52 (t, *J* = 11.0 Hz, 1 H), 2.61 (d, *J* = 14.0 Hz, 1 H), 2.59 (dd, *J* = 7.0, 5.5 Hz, 1 H), 2.18 (dd, *J* = 14.0, 4.0 Hz, 1 H), 2.13 (dd, *J* = 15.0, 5.5 Hz, 1 H), 1.38 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 171.9, 154.9, 84.0, 80.1, 76.6, 74.9, 74.7, 61.9 (× 2), 52.5, 52.4, 50.5, 43.9, 39.3, 28.3 (×3); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{28}NO_{12}S$ [(M + H)$^+$] 482.1332, found 482.1335.

Acetoxy Alcohol 31. To a solution of cyclic sulfate **30** (76.0 mg, 0.160 mmol) in DMF (2.0 mL) at room temperature was added cesium acetate (45.0 mg, 0.230 mmol). The resultant suspension was stirred at 65 °C for 6 h and then concentrated under reduced pressure to give an acetoxy sulfate as a pale yellow solid.

To a stirred suspension of the above acetoxy sulfate in THF (2.0 mL) at room temperature was added concentrated H_2SO_4 (4 drops). The mixture was stirred at room temperature for 1 h and then partitioned between ethyl acetate (5 mL) and ice−water (5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5 g, methanol:$CHCl_3$ = 3:97) afforded acetoxy alcohol **31** (68.0 mg, 83% for the two steps) as a white solid: $[\alpha]_D^{26}$ +18.3 (*c* 0.36, $CHCl_3$); IR (film) 3437, 2978, 2360, 1729, 1368, 1245, 1163, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.36 (d, *J* = 6.5 Hz, 1 H), 4.55 (s, 1 H), 4.26 (s, 1 H), 4.14 (s, 1 H), 4.07 (d, *J* = 4.0 Hz, 1 H), 3.79 (s, 1 H), 3.78 (dd, *J* = 10.5, 3.0 Hz, 1 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.67 (m, 1H), 2.56 (d, *J* = 14.0 Hz, 1 H), 2.44 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.19−2.15 (m, 2 H), 2.11 (s, 3 H), 1.84 (br s, 1H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 172.6, 171.3, 155.1, 83.7, 83.6, 74.7, 69.9, 66.1, 64.9, 55.5, 52.6, 52.4, 50.8, 42.9, 40.6, 28.3 (×3), 20.9; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{32}NO_{11}$ [(M + H)$^+$] 462.1975, found 462.1979.

Alcohol 32. To a solution of alcohol **31** (51.4 mg, 0.111 mmol) in CH_2Cl_2 (1.0 mL) at −20 °C were added pyridine (36.0 μL, 0.444

mmol) and DMAP (2.7 mg, 0.022 mmol), followed by trifluoromethanesulfonic acid anhydride (56.0 μL, 0.333 mmol). The resultant mixture was stirred at −20 °C for 2 h and then partitioned between ice−water (3.0 mL) and ethyl acetate (3.0 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a triflate as a yellow oil.

To a stirred solution of the above triflate in DMF (1.0 mL) at room temperature was added cesium acetate (63.90 mg, 0.333 mmol). The resultant mixture was stirred at room temperature for 4 h and then poured into a mixed solution of water and ethyl acetate (1:1, v/v, 10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5 g, methanol:$CHCl_3$ = 3:97) afforded alcohol **32** (36.4 mg, 71% for the two steps) as a colorless oil: $[\alpha]_D^{20}$ −6.6 (*c* 0.12, $CHCl_3$); IR (film) 3365, 2977, 2954, 2359, 2341, 1733, 1792, 1653, 1245 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (d, *J* = 7.0 Hz, 1 H), 4.85 (d, *J* = 2.0 Hz, 1 H), 4.33 (d, *J* = 6.0 Hz, 1 H), 4.03 (s, 1 H), 4.02 (s, 1 H), 3.97 (dd, *J* = 12.5, 3.5 Hz, 1 H), 3.90 (s, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.40 (d, *J* = 12.5 Hz, 1 H), 2.66 (d, *J* = 13.5 Hz, 1 H), 2.58 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.24 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.17 (s, 3 H), 2.15 (dd, *J* = 13.5, 4.5 Hz, 1 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 172.4, 171.2, 154.9, 83.5, 80.1, 78.7, 76.3, 68.4, 66.7, 65.8, 65.1, 52.7, 52.5, 43.8, 40.6, 28.3 (×3), 21.0; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{32}NO_{11}$ [(M + H)$^+$] 462.1975, found 462.1979.

Neodysiherbaine A (2). A solution of alcohol **32** (12.7 mg, 0.028 mmol) in aqueous 6 M HCl (0.5 mL) was heated at 85 °C overnight. The mixture was cooled to room temperature and lyophilized to afford **2** (8.5 mg, 93%) as a colorless solid: $[\alpha]_D^{20}$ +1.4 (*c* 0.07, H_2O); ^1H NMR (500 MHz, D_2O) δ 4.08 (br s, 1 H), 4.00 (br s, 1 H), 3.76 (t, *J* = 3.7 Hz, 1 H), 3.68 (dd, *J* = 13.0, 2.5 Hz, 1 H), 3.57 (br s, 1 H), 3.46 (d, *J* = 11.5 Hz, 1 H), 3.41 (d, *J* = 13.0 Hz, 1 H), 2.55 (dd, *J* = 15.0, 2.0 Hz, 1 H), 2.42 (d, *J* = 14.5 Hz, 1 H), 2.04 (dd, *J* = 14.3, 3.3 Hz, 1 H), 1.84 (dd, *J* = 15.0, 11.5 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O:CD_3OD = 15:1) δ 180.4, 174.1, 87.6, 81.6, 77.5, 70.4, 68.6, 67.8, 54.0, 45.3, 39.8; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{18}NO_8$ [(M + H)$^+$] 292.1032 found 292.1037.

8,9-*epi*-Neodysiherbaine A (4). A solution of **29b** (73.1 mg, 0.159 mmol) in aqueous 6 M HCl (1.0 mL) was heated at 65 °C overnight. The reaction mixture was cooled to room temperature and lyophilized to afford **4** (46.0 mg, 94%) as a white foam: $[\alpha]_D^{25}$ −40.0 (*c* 0.05, H_2O); ^1H NMR (600 MHz, D_2O) δ 4.13 (m, 1 H), 4.09 (m, 1 H), 4.05 (m, 1 H), 3.93 (ddd, *J* = 10.6, 5.0, 3.2 Hz, 1 H), 3.61 (dd, *J* = 10.6, 2.3 Hz, 1 H), 3.47 (dd, *J* = 10.6, 5.0 Hz, 1 H), 3.39 (dd, *J* = 10.6, 10.6 Hz, 1 H), 2.54 (d, *J* = 14.1 Hz, 1 H), 2.53 (dd, *J* = 15.6, 2.3 Hz, 1 H), 2.09 (dd, *J* = 14.1, 3.8 Hz, 1 H), 2.00 (dd, *J* = 15.6, 10.6 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O:CD_3OD = 15:1) δ 178.6, 174.1, 86.9, 84.0, 74.2, 67.4, 65.1, 64.4, 53.8, 44.3, 39.7; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{16}NO_8$ [(M − H)$^-$] 290.0876, found 290.0881.

8-*epi*-Neodysiherbaine A (5). A solution of **31** (50.0 mg, 0.108 mmol) in aqueous 6 M HCl (1.0 mL) was heated at 85 °C overnight. The mixture was cooled to room temperature and lyophilized to afford **5** (32.0 mg, 90%) as a white solid: $[\alpha]_D^{20}$ −20.6 (*c* 0.02, H_2O); ^1H NMR (500 MHz, D_2O) δ 4.17 (s, 1 H), 4.05 (s, 1 H), 3.93 (s, 1 H), 3.73 (d, *J* = 12.5 Hz, 1 H), 3.69 (d, *J* = 10.5 Hz, 1 H), 3.59 (d, *J* = 13.0 Hz, 1 H), 3.51 (s, 1 H), 2.68 (d, *J* = 15.0 Hz, 1 H), 2.49 (d, *J* = 14.0 Hz, 1 H), 2.19 (d, *J* = 13.5 Hz, 1 H), 2.02 (t, *J* = 12.5 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 180.5, 174.5, 88.0, 81.9, 75.1, 68.7, 67.0, 66.4, 54.5, 46.3, 40.3; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{18}NO_8$ [(M − H)$^-$] 290.0876, found 290.0876.

Pivalate 34. To a solution of diol **16** (24.2 mg, 0.0580 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C were added triethyamine (32.0 μL, 0.232 mmol) and DMAP (1.4 mg, 0.011 mmol) followed by pivaloyl chloride (21.0 μL, 0.173 mmol). The reaction mixture was stirred at −50 °C for 12 h and then poured into ice−water (ca. 1 mL). The mixture was extracted with ethyl acetate (3 × 3 mL), and the combined organic layers were washed with aqueous 1 M HCl (1 mL), saturated aqueous $NaHCO_3$ (1 mL), and brine (1 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5 g, methanol:$CHCl_3$ = 3:97) afforded pivalate **34** (23.1 mg, 79%) as a colorless oil: $[\alpha]_D^{17}$ +23.3 (*c* 0.06, $CHCl_3$); IR (film) 3446, 2973, 2359, 2342, 1733, 1717, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.33 (d, *J* = 7.0 Hz, 1 H), 5.19 (m, 1 H), 4.32 (d, *J* = 7.0 Hz, 1 H), 4.22 (s, 1 H), 4.14 (s, 1 H), 4.02 (s, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.61 (dd, *J* = 11.0, 5.5 Hz, 1 H), 3.49 (t, *J* = 11.0 Hz, 1 H), 2.58−2.54 (m, 2 H), 2.17 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.08−2.04 (m, 2 H), 1.40 (s, 9 H), 1.18 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3 (×2), 172.6, 155.3, 84.4, 82.7, 80.2, 73.8, 67.7, 66.4, 61.4, 52.7, 52.6, 51.1, 44.5, 40.3, 39.1, 28.5 (×3), 27.4 (×3); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{38}NO_{11}$ [(M + H)$^+$] 504.2445, found 504.2452.

Acetate 35. To a solution of **34** (22.0 mg, 0.0430 mmol) in CH_2Cl_2 (0.5 mL) at −20 °C were added pyridine (14.0 μL, 0.172 mmol) and DMAP (1.2 mg, 0.0080 mmol) followed by trifluoromethanesulfonic acid anhydride (22.0 μL, 0.133 mmol). The reaction mixture was stirred at −20 °C for 2 h and then partitioned between ice−water (1.5 mL) and ethyl acetate (1.5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a triflate as a yellow oil.

To a solution of the above triflate in DMF (0.5 mL) at room temperature was added cesium acetate (75.0 mg, 0.387 mmol). The resultant mixture was stirred at 50 °C for 48 h and then poured into a mixed solution of water and ethyl acetate (1:1, v/v, 5.0 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5 g, ethyl acetate:hexanes = 3:7) afforded acetate **35** (8.6 mg, 37% for the two steps) and **36** (2.1 mg, 11% for the two steps) as colorless oils. Data for **35**: $[\alpha]_D^{17}$ +98.8 (*c* 0.085, $CHCl_3$); IR (film) 2974, 2876, 2359, 1733, 1717, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, *J* = 7.0 Hz, 1 H), 5.35 (dt, *J* = 10.5, 5.0 Hz, 1 H), 5.13 (dd, *J* = 10.5, 3.5 Hz, 1 H), 4.31 (s, 1 H), 4.29 (d, *J* = 7.0 Hz, 1 H), 4.09 (s, 1H), 3.89 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.81 (s, 3 H), 3.67 (s, 3 H), 3.11 (t, *J* = 10.5 Hz, 1 H), 2.64 (d, *J* = 13.0 Hz, 1 H), 2.58 (dd, *J* = 14.5, 4.5 Hz, 1 H), 2.16 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.12 (s, 3H), 2.05 (m, 1 H), 1.41 (s, 9 H), 1.13 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 174.9, 174.3, 172.3, 155.1, 84.9, 79.6, 71.4, 66.6, 66.0 (×2), 60.3, 52.6, 52.2, 51.0, 44.7, 39.9, 38.7, 28.3 (×3), 26.9 (×3), 20.9; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{40}NO_{12}$ [(M + H)$^+$] 546.2551, found 546.2557. Data for **36**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (d, *J* = 4.5 Hz, 1H), 5.39 (d, *J* = 6.0 Hz, 1H), 4.37 (m, 1H), 4.31 (d, *J* = 5.5 Hz, 1H), 4.12 (d, *J* = 15.0 Hz, 1H), 4.06 (s, 1H), 3.86 (d, *J* = 15.0 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.62 (d, *J* = 13.5 Hz, 1H), 2.53 (dd, *J* = 14.5, 5.5 Hz, 1H), 2.23 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.19 (dd, *J* = 14.5, 5.5 Hz, 1H), 1.41 (s, 9H), 1.21 (s, 9H).

9-*epi*-Neodysiherbaine A (6). A solution of **35** (6.00 mg, 0.0109 mmol) in aqueous 6 M HCl (1.0 mL) was heated at 100 °C overnight. The mixture was cooled to room temperature and lyophilized to afford **6** (4.4 mg, 100%) as a white foam: $[\alpha]_D^{22}$ +33.1 (*c* 0.12, H_2O); ^1H NMR (500 MHz, D_2O) δ 4.29 (m, 1 H), 4.17 (s, 1 H), 3.88 (dd, *J* = 11.0, 3.0 Hz, 1 H), 3.82 (dt, *J* = 11.0,

4.5 Hz, 1 H), 3.69 (dd, J = 11.0, 4.5 Hz, 1 H), 3.65 (dd, J = 10.5, 4.5 Hz, 1 H), 3.07 (t, J = 10.5 Hz, 1 H), 2.63 (dd, J = 13.0, 2.5 Hz, 1 H), 2.62 (d, J = 13.5 Hz, 1 H), 2.15 (dd, J = 13.0, 3.5 Hz, 1 H), 2.10 (dd, J = 13.5, 11.0 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O:CD_3OD = 15:1) δ 181.0, 175.9, 89.0, 78.8, 77.3, 71.4, 65.1, 54.9, 46.9, 40.5, 31.6; HRMS (FAB) m/z calcd for $C_{11}H_{16}NO_8$ [(M − H)$^-$] 290.0876, found 290.0883.

Thiocarbonate 37. To a solution of alcohol **31** (46.0 mg, 0.0990 mmol) in toluene (2.0 mL) at room temperature were added DMAP (24.0 mg, 0.198 mmol) and phenyl chlorothionoformate (0.0210 mL, 0.149 mmol). The resultant mixture was heated at reflux for 3 h and then cooled to room temperature. Water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were successively washed with aqueous 1 M HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5 g, ethyl acetate:hexanes = 1:1) afforded thiocarbonate **37** (41.0 mg, 70%) as a white solid: $[\alpha]_D^{26}$ +25.3 (*c* 0.06, $CHCl_3$); IR (film) 3365, 2951, 2359, 1734, 1717, 1276, 1200 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, J = 8.0 Hz, 2 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 2 H), 5.68 (s, 1 H), 5.26 (d, J = 7.5 Hz, 1 H), 4.81 (d, J = 1.5 Hz, 1 H), 4.32 (dd, J = 7.5, 5.0 Hz, 1 H), 4.14 (s, 1 H), 3.99 (s, 1 H), 3.89 (d, J = 13.0 Hz, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.72 (dd, J = 10.5, 3.0 Hz, 1 H), 2.77 (d, J = 14.0 Hz, 1 H), 2.46 (dd, J = 14.0, 4.5 Hz, 1 H), 2.21 (dd, J = 15.0, 6.0 Hz, 1 H), 2.17 (dd, J = 13.5, 4.5 Hz, 1 H), 2.16 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 172.7, 172.1, 170.5, 155.1, 153.3, 129.6 (×2), 126.7, 121.7 (×2), 84.2, 79.9, 76.7, 74.8, 74.4, 65.7, 64.7, 52.6, 52.4, 50.6, 43.5, 40.4, 28.2 (×3), 20.9; HRMS (FAB) m/z calcd for $C_{27}H_{36}NO_{12}S$ [(M + H)$^+$] 598.1958, found 598.1960.

Acetate 38. A solution of thiocarbonate **37** (41.0 mg, 0.069 mmol) and AIBN (23.0 mg, 0.138 mmol) in toluene (3.0 mL) was degassed by bubbling of argon under sonication for 30 min. To the mixture heated at 130 °C was added Bu_3SnH (0.110 mL, 0.414 mmol). The resultant mixture was stirred at 130 °C for 1 h, cooled to room temperature, and then concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5 g, ethyl acetate:hexanes = 7:3) afforded acetate **38** (24.0 mg, 78%) as a white solid: $[\alpha]_D^{26}$ +34.4 (*c* 0.05, $CHCl_3$); IR (film) 3365, 2952, 2359, 1728, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (d, J = 7.0 Hz, 1 H), 4.68 (s, 1 H), 4.28 (dd, J = 7.5, 5.0 Hz, 1 H), 3.90 (dd, J = 13.0, 3.0 Hz, 1 H), 3.89 (d, J = 9.0 Hz, 1 H), 3.88 (m, 1H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.44 (dd, J = 11.0, 1.5 Hz, 1 H), 2.67 (d, J = 15.0 Hz, 1 H), 2.40 (dd, J = 14.0, 4.5 Hz, 1 H), 2.34 (d, J = 17.0 Hz, 1 H), 2.16 (dd, J = 16.0, 7.0 Hz, 1 H), 2.15 (d, J = 7.0 Hz, 1 H), 2.11 (s, 3 H), 1.92 (dt, J = 11.5, 4.0 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 172.3, 171.3, 155.1, 83.7, 76.2, 74.7, 67.5 (×2), 64.8, 52.4 (×2), 50.9, 43.8, 40.2, 28.3 (×3), 28.2, 21.3; HRMS (FAB) m/z calcd for $C_{20}H_{32}NO_{10}$ [(M + H)$^+$] 446.2026, found 446.2029.

8-Deoxyneodysiherbaine A (7). A solution of acetate **38** (35.0 mg, 0.079 mmol) in aqueous 6 M HCl (1.0 mL) was heated at 85 °C overnight. The mixture was cooled to room temperature and lyophilized to afford **7** (22.0 mg, 92%) as a white solid: $[\alpha]_D^{20}$ −37.0 (*c* 0.016, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 4.16 (s, 1 H), 4.08 (s, 1 H), 3.89 (dd, J = 11.0, 3.0 Hz, 1 H), 3.76 (s, 1 H), 3.69 (d, J = 13.0 Hz, 1 H), 3.53 (d, J = 12.5 Hz, 1 H), 2.74 (dd, J = 15.5, 3.0 Hz, 1 H), 2.46 (d, J = 15.0 Hz, 1 H), 2.26 (dd, J = 14.5, 3.5 Hz, 1 H), 2.19 (dd, J = 14.5, 2.0 Hz, 1 H), 2.08 (dd, J = 15.0, 10.5 Hz, 1 H), 1.95 (dt, J = 15.5, 3.0 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O:CD_3OD = 15:1) δ 178.9, 174.8, 87.6, 83.6, 78.5, 74.1, 69.7, 68.0, 54.5, 45.3, 40.3; HRMS (FAB) m/z calcd for $C_{11}H_{16}NO_8$ [(M − H)$^-$] 274.0927, found 274.0923.

8β-Alcohol 39. To a solution of cyclic sulfate **30** (89.9 mg, 0.180 mmol) in *N*,*N*-dimethylacetamide (2.0 mL) at room temperature was added $NaBH_4$ (17.0 mg, 0.450 mmol). The resultant mixture was stirred at room temperature for 4.5 h and then concentrated under reduced pressure to give a sulfate monoester as a white solid.

To a suspension of the above sulfate in THF (2.0 mL) at room temperature was added concentrated H_2SO_4 (9 drops). The resultant mixture was stirred at room temperature for 1 h and then partitioned between ethyl acetate (5 mL) and ice−water (5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (5 g, methanol:$CHCl_3$ = 2:98) afforded 8β-alcohol **39** (37.0 mg, 51% for the two steps) as a white solid: $[\alpha]_D^{20}$ +1.3 (*c* 0.08, $CHCl_3$); IR (film) 3441, 2953, 2359, 2341, 1734, 1714, 1164, 1074 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (d, J = 7.0 Hz, 1 H), 4.31 (dd, J = 7.5, 5.0 Hz, 1 H), 4.17 (s, 1 H), 4.13 (s, 1 H), 3.72 (s, 1H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.67 (dd, J = 13.0, 1.5 Hz, 1 H), 3.55 (ddd, J = 11.0, 4.0, 1.5 Hz, 1 H), 2.55 (d, J = 14.0 Hz, 1 H), 2.49 (dd, J = 14.0, 5.0 Hz, 1 H), 2.21 (dt, J = 13.0, 4.0 Hz, 1 H), 2.15 (dd, J = 15.0, 6.0 Hz, 1 H), 2.05 (dd, J = 10.0, 4.0 Hz, 1 H), 1.82 (dd, J = 14.5, 3.5 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 171.5, 155.4, 84.2, 81.2, 80.2, 73.3, 64.1, 60.4, 52.5, 52.4, 51.1, 44.5, 40.4, 28.6, 28.3 (×3); HRMS (FAB) m/z calcd for $C_{18}H_{30}NO_9$ [(M + H)$^+$] 404.1942, found 404.1942.

8α-Alcohol 40. To a solution of alcohol **39** (37.0 mg, 0.0920 mmol) in CH_2Cl_2 (2.0 mL) at room temperature were added powdered 4 Å molecular sieves (50.0 mg), NMO (32.0 mg, 0.28 mmol), and TPAP (6.50 mg, 0.018 mmol). The resultant mixture was stirred at room temperature for 30 min and then passed through a short pad of silica gel (5 g, ethyl acetate). The filtrate was concentrated under reduced pressure to give a ketone (22.6 mg) as a white solid.

To a stirred solution of the above ketone in methanol (1.0 mL) at −20 °C was added $NaBH_4$ (6.10 mg, 0.16 mmol). The resultant mixture was stirred at −20 °C for 15 min and then poured into a mixed solution of CH_2Cl_2 and pH 7 phosphate buffer (3:1, v/v, 4.0 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10 g, methanol:$CHCl_3$ = 3:97) afforded 8α-alcohol **40** (23.0 mg, 88% for the two steps) as a white solid: $[\alpha]_D^{20}$ +115.3 (*c* 0.045, $CHCl_3$); IR (film) 3375, 2955, 2359, 2341, 1734, 1717, 1164 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (d, J = 7.5 Hz, 1 H), 4.32 (dd, J = 12.5, 5.0 Hz, 1 H), 3.99 (s, 1 H), 3.96 (s, 1 H), 3.78 (ddd, J = 11.0, 4.0, 2.0 Hz, 1 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.23 (t, J = 11.0 Hz, 1 H), 3.72 (m, 1 H), 2.66 (dd, J = 14.0, 5.0 Hz, 1 H), 2.61 (d, J = 13.0 Hz, 1 H), 2.28 (d, J = 11.0 Hz, 1 H), 2.21 (dd, J = 14.0, 4.0 Hz, 1 H), 2.08 (dd, J = 14.0, 4.0 Hz, 1 H), 1.95 (dq, J = 12.5, 5.0 Hz, 1 H), 1.67 (dd, J = 12.0, 5.0 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 172.7, 154.9, 83.5, 80.4, 79.9, 76.4, 67.6, 64.9, 52.6, 52.3, 50.9, 45.8, 40.8, 29.4, 28.3 (×3); HRMS (FAB) m/z calcd for $C_{18}H_{30}NO_9$ [(M + H)$^+$] 404.1942, found 404.1923.

9-Deoxyneodysiherbaine A (8). A solution of alcohol **40** (41.0 mg, 0.101 mmol) in aqueous 6 M HCl (1.0 mL) was heated at 65 °C overnight. The mixture was cooled to room temperature and lyophilized to afford **8** (30.0 mg, 90%) as a brown solid: $[\alpha]_D^{20}$ +18.4 (*c* 0.026, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 4.13 (s, 1H), 4.05 (s, 1H), 3.89 (ddd, J = 12.0, 5.0, 3.5 Hz, 1H), 3.74 (ddd, J = 12.5, 3.0, 1.5 Hz, 1H), 3.65 (dd, J = 12.0, 2.0 Hz, 1H), 3.30 (t, J = 12.0 Hz, 1H), 2.57 (d, J = 13.0 Hz, 1H), 2.54 (dd, J = 14.5, 2.5 Hz, 1H), 2.08 (dd, J = 14.0, 3.0 Hz, 1H), 2.03 (dd, J = 15.0, 12.0 Hz, 1H), 1.83 (dq, J = 12.0, 4.5 Hz, 1H), 1.57 (dd, J = 12.5, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, D_2O:CD_3OD = 15:1) δ 178.5, 174.6, 87.4, 82.3, 77.9, 73.4, 68.8, 66.5, 54.3, 45.5, 40.3; HRMS (FAB) m/z calcd for $C_{11}H_{16}NO_8$ [(M − H)$^-$] 274.0927, found 274.0927.

Cyclic Thiocarbonate 41. To a solution of diol **16** (624 mg, 1.49 mmol) in toluene (15 mL) at 0 °C were added DMAP (182 mg, 1.49 mmol) and thiocarbonyl diimidazole (320 mg, 1.79 mmol).

The resultant mixture was heated at 70 °C for 30 min and then concentrated under reduced pressure. Purification by flash column chromatography on silica gel (20 g, ethyl aceate:hexanes = 3:7) afforded cyclic thiocarbonate **41** (523 mg, 76%) as a colorless solid: $[\alpha]_D^{20}$ +36.9 (*c* 0.79, $CHCl_3$); IR (film) 3421, 2978, 1745, 1713, 1499, 1353, 1320, 1164, 1095, 991, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, J = 6.5 Hz, 1 H), 5.12 (d, J = 7.0 Hz, 1 H), 5.02 (ddd, J = 8.0, 6.0, 2.5 Hz, 1 H), 4.34 (s, 2 H), 4.27 (t, J = 4.5 Hz, 1 H), 3.98 (dd, J = 12.5, 6.0 Hz, 1 H), 3.72 (s, 3 H), 3.70 (s, 3 H), 3.28 (dd, J = 12.5, 8.0 Hz, 1 H), 2.61 (dd, J = 14.5, 5.5 Hz, 1 H), 2.56 (d, J = 14.0 Hz, 1 H), 2.27 (dd, J = 14.0, 5.0 Hz, 1 H), 2.17 (dd, J = 14.5, 4.5 Hz, 1 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 173.6, 172.2, 155.2, 109.9, 84.1, 80.4, 75.4, 75.1, 74.2, 62.2, 52.9, 52.8, 50.9, 44.9, 39.4, 28.5 (×3); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{28}NO_{10}S$ [(M + H)$^+$] 462.1434, found 462.1434.

Olefin 42. To a solution of cyclic thiocarbonate **41** (525 mg, 1.13 mmol) in THF (0.6 mL) at room temperature was added 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (0.62 mL, 3.41 mmol). The resultant mixture was stirred at 40 °C for 12 h. The mixture was cooled to room temperature and purified by flash column chromatography on silica gel (20 g, ethyl acetate:hexanes = 1:1) to afford olefin **42** (319 mg, 73%) as colorless oil: $[\alpha]_D^{20}$ −143.7 (*c* 0.41, $CHCl_3$); IR (film) 3375, 2977, 2359, 2342, 1748, 1733, 1716, 1166, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96−5.91 (m, 2 H), 5.39 (d, J = 6.5 Hz, 1 H), 4.20 (m, 1 H), 4.04 (m, 1 H), 4.00−3.86 (m, 3 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 2.51 (d, J = 14.0 Hz, 1 H), 2.42 (dd, J = 14.0, 5.0 Hz, 1 H), 2.14 (dd, J = 14.0, 5.0 Hz, 1 H), 2.11 (dd, J = 14.0, 6.5 Hz, 1 H), 1.32 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 172.2, 154.9, 130.4, 121.9, 84.0, 79.6, 74.6, 73.5, 63.5, 52.2, 52.1, 50.7, 43.9, 39.4, 28.0 (×3); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{28}NO_8$ [(M + H)$^+$] 386.1815, found 386.1816.

Compound 3. To a solution of olefin **42** (167 mg, 0.430 mmol) in hexane/methanol (2:1, v/v, 6 mL) at room temperature was added $Pd(OH)_2$/C (10 wt %, 16.7 mg). The mixture was stirred at room temperature under a hydrogen atmosphere for 4 h and then filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10 g, ethyl acetate:hexanes = 1:1) to afford fully protected glutamic acid derivative (158 mg, 94%) as a white solid: $[\alpha]_D^{20}$ +107.0 (*c* 0.22, $CHCl_3$); IR (film) 3375, 2952, 2359, 1750, 1716, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (d, J = 7.0 Hz, 1 H), 4.38 (d, J = 5.5 Hz, 1 H), 3.89 (s, 1 H), 3.83 (s, 1 H), 3.69 (s, 3 H), 3.60 (s, 3 H), 3.75 (ddt, J = 10.5, 4.0, 2.0 Hz, 1 H), 3.26 (dt, J = 13.0, 2.0 Hz, 1 H), 2.54 (d, J = 14.0 Hz, 1 H), 2.31 (dd, J = 14.0, 4.5 Hz, 1 H), 2.16 (dd, J = 14.0, 6.0 Hz, 1 H), 2.06−2.03 (m, 2 H), 1.96 (dq, J = 13.0, 4.0 Hz, 1 H), 1.64 (tt, J = 13.5, 4.0 Hz, 1 H), 1.38 (s, 9 H), 1.27 (d, J = 13.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 172.4, 155.1, 83.9, 79.7, 77.2, 77.1, 75.6, 66.2, 52.2, 52.1, 50.9, 44.9, 40.1, 28.2 (×2), 25.3, 19.5; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{30}NO_8$ [(M + H)$^+$] 388.1971, found 388.1971.

A solution of the above product (155 mg, 0.40 mmol) in aqueous 6 M HCl (1.0 mL) was heated at 65 °C overnight. The mixture was cooled to room temperature and lyophilized to afford compound **3** (100 mg, 85%) as a brown solid: $[\alpha]_D^{20}$ −21.7 (*c* 0.026, H_2O); ^1H NMR (500 MHz, D_2O) δ 4.07 (s, 1 H), 3.97 (s, 1 H), 3.88 (dd, J = 10.5, 3.0 Hz, 1 H), 3.72 (d, J = 7.5 Hz, 1 H), 3.69 (dd, J = 10.5, 3.5 Hz, 1 H), 3.29 (t, J = 11.0 Hz, 1 H), 2.62 (dd, J = 15.5, 3.0 Hz, 1 H), 2.52 (d, J = 14.0 Hz, 1 H), 2.15−2.09 (m, 2 H), 1.97 (d, J = 11.0 Hz, 1 H), 1.71−1.69 (m, 2 H), 1.30 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O:CD_3OD = 15:1) δ 178.8, 173.5, 86.4, 79.9, 77.0, 67.8, 53.3, 46.1, 39.8, 25.8, 20.8; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{17}NO_6Cl$ [(M − H)$^-$] 294.0774, found 294.0750.

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Supporting Information Available: Experimental procedures and characterization data for compounds in Scheme 5 and copies of ^1H and ^{13}C NMR spectra for compounds **2**−**8**, **11**, **16**−**20**, **23**−**27**, **29**−**32**, **34**, **35**, and **37**−**42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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