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Rapid and Efficient Synthesis of Dysiherbaine and Analogues to Explore Structure−Activity Relationships

Makoto Sasaki,*,† Koichi Tsubone,† Kunimori Aoki,† Nobuyuki Akiyama,† Muneo Shoji,† Masato Oikawa,† Ryuichi Sakai,‡ and Keiko Shimamoto§

Graduate School of Life Sciences, Tohoku University, Sendai 981-8555, Japan, School of Fisheries Sciences, Kitasato University, Sanriku-cho, Iwate 022-0101, Japan, and Suntory Institute for Bioorganic Research (SUNBOR), Mishima-gun, Osaka 618-8503, Japan

masasaki@bios.tohoku.ac.jp

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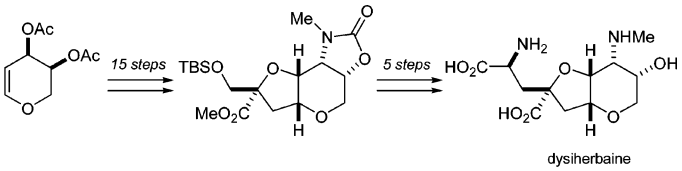

A rapid and efficient total synthesis of dysiherbaine (**1**), a potent and subtype-selective agonist for ionotropic glutamate receptors, has been accomplished. A key intermediate **15** was synthesized by two approaches. The first synthetic route utilized compound **9**, an advanced intermediate in our previous total synthesis of neodysiherbaine A, as the starting point, and the cis-oriented amino alcohol functionality on the tetrahydropyran ring was installed by using an intramolecular S_N2 cyclization of *N*-Boc-protected amino alcohol **20**. An alternative and even more efficient synthetic approach to **15** featured stereoselective introduction of an amino group at C8 by iodoaminocyclization prior to constructing the bicyclic ether skeleton. The amino acid appendage was efficiently constructed by a catalytic asymmetric hydrogenation of enamide ester **36**. The synthetic route developed here provided access to several dysiherbaine analogues, including 9-*epi*-dysiherbaine (**38**), 9-deoxydysiherbaine (**39**), 9-methoxydysiherbaine (**40**), and *N*-ethyldysiherbaine (**41**). The preliminary structure−activity relationship studies revealed that the presence and stereochemistry of the C9 hydroxy group in dysiherbaine is important for high-affinity and selective binding to glutamate subtype receptors.

Introduction

Ionotropic glutamate receptors (iGluRs) form a family of ligand-gated ion channels that mediate fast synaptic transmission in the mammalian central nervous system.[1] The iGluRs can be divided, based on their affinities for the selective agonists, into three subclasses: *N*-methyl-D-aspartate (NMDA), (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), and kainate (KA) receptors. These receptors play important roles in many processes, including learning and memory, and are also implicated in a number of neuronal disorders. There are seven NMDA receptor genes (NR1, NR2A-2D, NR3A, and NR3B), four AMPA receptor genes (GluR1−4), and five KA receptor genes (GluR5−7 and KA1−2). This diversity makes the functional analysis of native glutamate receptors a formidable task. Therefore, the development of selective ligands that can discriminate between different glutamate receptors has been the focus of extensive research.

Dysiherbaine (**1**)[2] and its natural congener, neodysiherbaine A (**2**),[3] isolated by Sakai and co-workers from the Micronesian sponge *Dysidea herbacea*, are remarkable excitatory amino acids with potent convulsant activity (Figure 1).[4] Structurally, these amino acids consist of a cis-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamic acid substructure. Dysiherbaine activates the AMPA and KA classes of receptors, with a higher affinity for the latter, but shows no detectable affinity

† Tohoku University.
‡ Kitasato University.
§ Suntory Institute for Bioorganic Research (SUNBOR).

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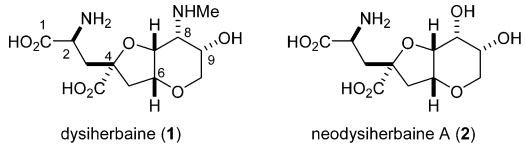
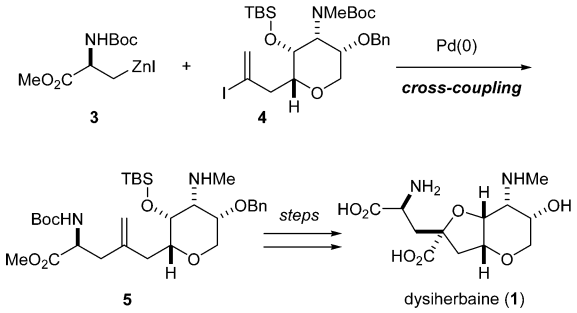


FIGURE 1. Structures of dysiherbaine and neodysiherbaine A.

for NMDA receptors.[5] Furthermore, it has been revealed that dysiherbaine had extremely high affinity for recombinant GluR5 or GluR6 KA receptors but very low affinity for KA2 receptors, and this difference of affinities produced unusual biophysical behavior from heteromeric KA receptors.[6] Neodysiherbaine A is also a selective agonist for AMPA and KA receptors, with slightly different binding affinities for KA receptor subunits, but its affinity for GluR5 and GluR6 is 15- to 25-fold lower than that of dysiherbaine.[7] The high affinity and selectivity of dysiherbaines for certain KA receptor subtypes made these natural products useful tools for exploring the complex biophysical functions of glutamate receptor ion channels.[8] Furthermore, dysiherbaine is capable of inducing long-lasting epileptic-like seizures in mice. This unique in vivo profile was not reproduced by other excitatory amino acids such as kainic acid or domoic acid, which are often used to generate seizures in model animals.[5] Therefore, dysiherbaine may replace the currently used seizurogenic drugs in brain research, providing a feasible synthetic supply of the drug.

In addition to their unique biological profiles, the intriguing chemical structures of dysiherbaines have attracted considerable attention from synthetic chemists. Thus, a number of synthetic efforts have been described, including five total and one formal syntheses of dysiherbaine, four total syntheses of neodysiherbaine A, and structure−activity relationship (SAR) studies of neodysiherbaine A from this laboratory.[3,9−12] We describe herein a full account of a rapid and efficient total synthesis of dysiherbaine (**1**).[13] In addition, we detail the preparation and preliminary biological evaluation of several dysiherbaine analogues to elucidate the detailed SAR profile.

SCHEME 1. First-generation Total Synthesis of Dysiherbaine (1)



Results and Discussion

Synthesis of the Key Intermediate. We previously reported the total synthesis of dysiherbaine (**1**), which involved as a key feature the palladium(0)-catalyzed cross-coupling reaction of organozinc compound **3** with vinyl iodide **4** based on Jackson's protocol.[9b] Whereas overall the synthetic route was convergent, this first-generation synthesis required a multistep sequence of reactions (27 longest linear steps from the known 1,6:2,3-dianhydrohexose,[14] which is available in five steps from 1,6-anhydro-D-glucose, and 2.2% overall yield) and created a stereochemical problem with respect to constructing the C4 quaternary stereocenter (Scheme 1).

Recently, we developed an efficient synthetic route to neodysiherbaine A (**2**) and its structural variants with respect to the C8 and C9 functionalities.[10d,11b] The advanced key intermediate **10** was utilized as a branching point for the diverted total synthesis (Scheme 2). The synthesis of **10** featured (i) stereoselective *C*-glycosylation to set the C6 stereocenter (**6** + **7** → **8**), (ii) a concise synthesis of the bicyclic ether skeleton **9**, and (iii) stereoselective construction of the amino acid appendage through a catalytic asymmetric hydrogenation of enamide ester.

Initially, we proposed alcohol **11**[10d] as a viable precursor to dysiherbaine (**1**). Thus, we first explored the possibility of installing an *N*-methyl group at C8 by oxidation of alcohol **11** followed by reductive amination of the resultant ketone **12** (Scheme 3). However, this sequence was abandoned due to the poor yield of the desired **13** (16% yield for the two steps). The observed poor yield of the reductive amination was in good agreement with the results reported by Chamberlin and coworkers in a closely related system.[9d] Alternatively, treatment of **11** under Mitsunobu reaction conditions with diphenylphosphoryl azide (DPPA)[15] followed by hydrogenation produced the desired amine **14** only in a low yield (26%, two steps).

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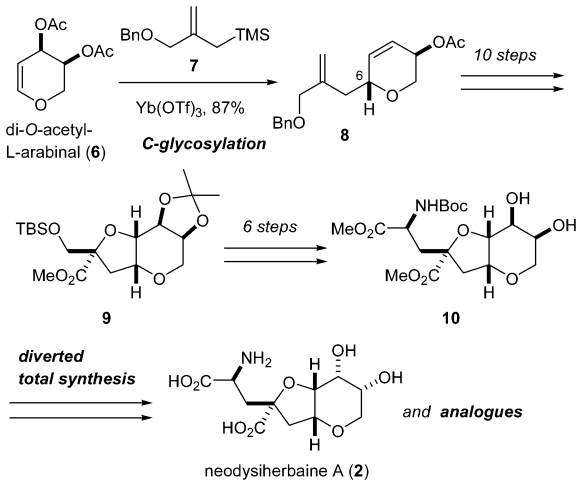
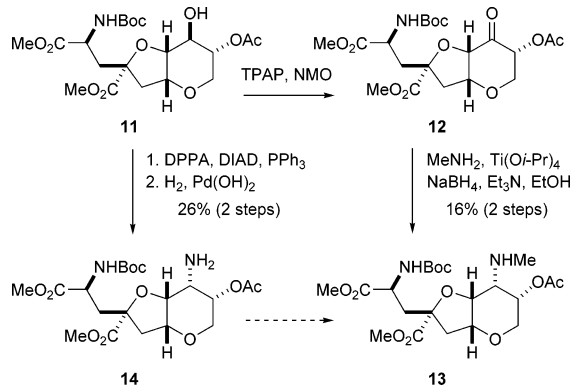
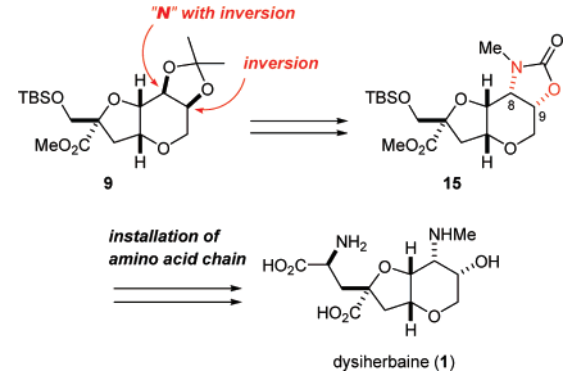
SCHEME 2. Diverted Total Synthesis of Neodysiherbaine A (2) and Its Analogue



SCHEME 3. First Attempts to Introduce a C8 Amino Group



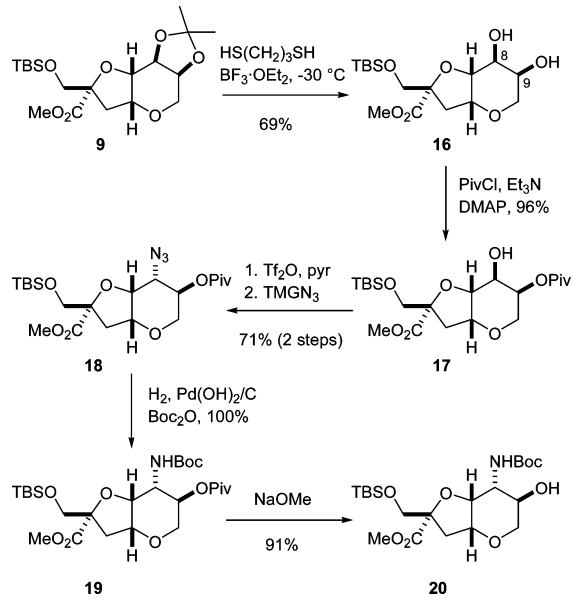
SCHEME 4. New Synthetic Strategy



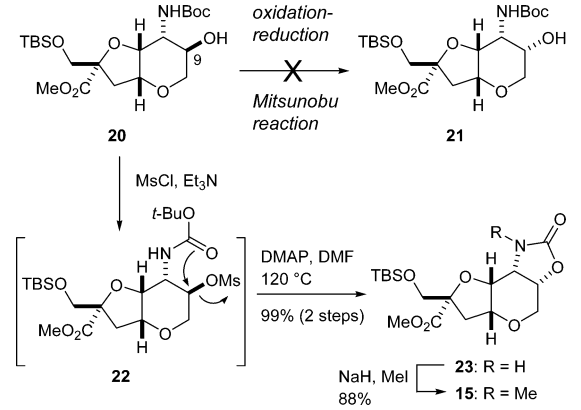
Nucleophilic displacement of a leaving group at C8 with azide ion was also unsuccessful, probably due to a severe torsional interaction with the axial substituents at C7 and C9.

In light of these preliminary unsuccessful results, we decided to install the C8 amino group on the relatively early stage intermediate and set, as our next goal, the synthesis of key compound **15** starting from **9**[10d,11b] (Scheme 4). After some experimentation, the acetonide from ester **9** was selectively deprotected by exposure to 1,3-propanedithiol in the presence of boron trifluoride etherate (CH_2Cl_2, −30 °C) to afford diol **16** in 69% yield (Scheme 5). Subsequent treatment of diol **16** with pivaloyl chloride and triethylamine (CH_2Cl_2, −78 °C) afforded monopivaloate ester **17** selectively (96%) due to the

SCHEME 5. Stereoselective Introduction of a C8 Amino Group



SCHEME 6. Synthesis of Key Intermediate 15

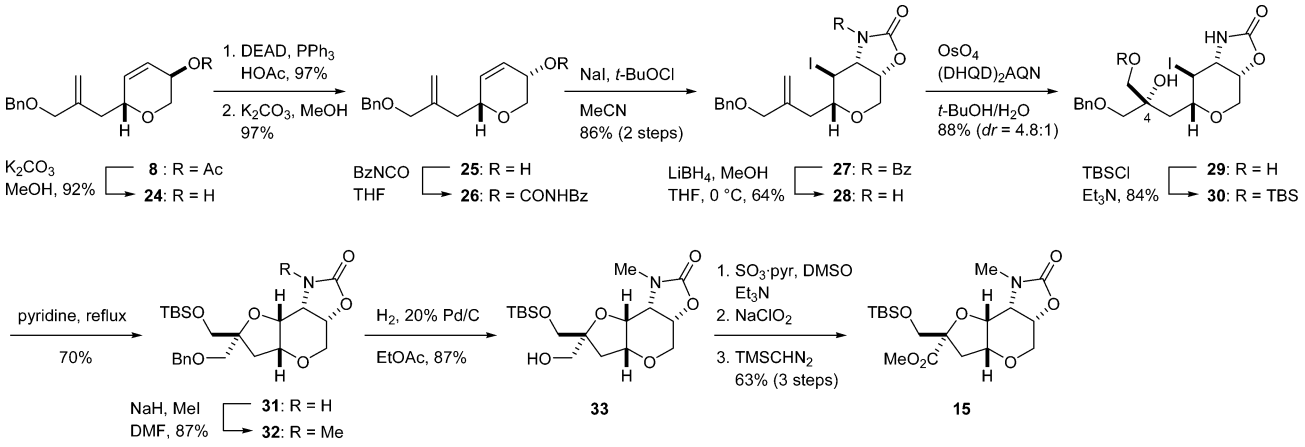


equatorial disposition of the C9 alcohol, as well as the steric congestion of the axial-oriented C8 alcohol. The remaining alcohol in **17** was converted to the corresponding triflate (trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2, −20 °C), which was then treated with tetramethylguanidium azide (DMF, 35 °C). Smooth nucleophilic displacement took place to provide the desired azide **18** in 71% yield for the two steps. Hydrogenation of **18** in the presence of di-*tert*-butyl dicarbonate proceeded cleanly to afford *N*-*tert*-butoxycarbonyl (Boc) derivative **19** in quantitative yield. Finally, removal of the pivaloyl group (NaOMe, MeOH) led to alcohol **20** in 91% yield.

Having successfully introduced an amino group at C8, we were now in a position to invert the C9 hydroxy group. We first attempted to perform this transformation (**20** → **21**) by oxidation−reduction sequence or Mitsunobu reaction, but all of these attempts were unsuccessful (Scheme 6). Accordingly, we next opted for the inversion by an intramolecular cyclization. Benedetti and Norbedo reported facile inversion of vicinal *N*-Boc-amino alcohols via S_N2 cyclization to form oxazolidinones.[16] Thus, alcohol **20** was treated with methanesulfonyl chloride and triethylamine (CH_2Cl_2, 0 °C), whereupon the

(16) Benedetti, F.; Norbedo, S. *Tetrahedron Lett.* **2000**, *41*, 10071−10074.

SCHEME 7. Improved Synthesis of Key Intermediate 15

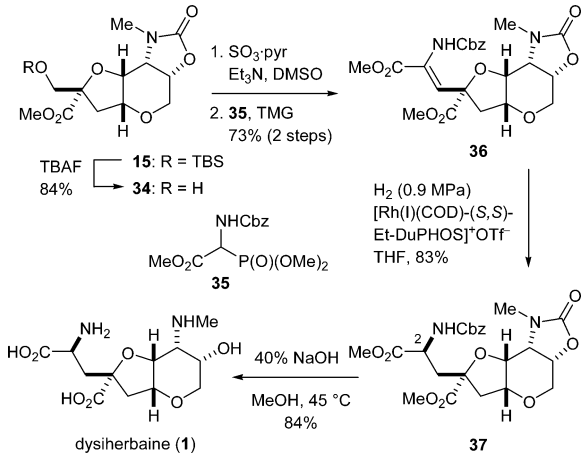


resulting crude mesylate **22** was heated with dimethylaminopyridine in DMF at 120 °C (Scheme 6). The desired oxazolidinone **23** was obtained in nearly quantitative yield for the two steps. Subsequent *N*-methylation (NaH, MeI, DMF) provided compound **15** in 88% yield.

Although we secured the synthetic route to compound **15**, we sought an alternative and even more efficient synthesis of this key intermediate. In the new synthetic approach, we planned to introduce the C8,C9 cis-amino alcohol functionality prior to constructing the bicyclic ether skeleton. The synthesis started with inversion of the stereochemistry at C9 in acetate **8**[10d,11b] (Scheme 7). After removal of the acetyl group from **8** (K_2CO_3, MeOH, 92%), the hydroxy group of the resultant **24** was inverted by Mitsunobu reaction (DEAD, PPh_3, HOAc, 97%),[17] giving the corresponding acetate. Subsequent deacetylation provided the desired alcohol **25** in 97% yield. Next, we attempted to install an amino functionality into the C8 position by iodoaminocyclization.[18−20] Thus, treatment of **25** with benzoyl isocyanate (THF, room temperature) provided the corresponding *N*-benzoyl carbamate **26**, which was then subjected to iodocyclization. Reaction of **26** with iodine in the presence of $LiAl(Ot\text{-}Bu)_4$ in THF/toluene[18] did not proceed, probably due to the low nucleophilicity of the nitrogen atom of **26**. The reaction of **26** with *N*-iodosuccinimide (NIS) and sodium hydride yielded the desired oxazolidinone **27** in modest yields (37−50%). It was eventually found that the best result was obtained by treatment of **26** with *tert*-butyl hypoiodite, generated in situ from sodium iodide and *tert*-butyl hypochlorite, in acetonitrile at room temperature.[20] Under these conditions, the desired **27** was obtained in 86% yield for the two steps from **25**.

The benzoyl group in **27** was reductively removed ($LiBH_4$, MeOH, THF, 64%)[21] and the resultant exo-olefin **28** was then subjected to asymmetric dihydroxylation with OsO_4 and $(DHQD)_2AQN$ ligand.[10d,22] The expected diol **29** was obtained in 88% yield and good diastereoselectivity (dr = ca. 4.8:1). Selective protection of the primary alcohol in **29** as its *tert*-butyldimethylsilyl (TBS) ether under standard conditions (TBSCl, Et_3N, 84%), followed by heating the resultant **30** in pyridine at reflux, afforded bicyclic ether skeleton **31** in 70% yield. At this stage, the undesired diastereomer at C4 was readily separated from the desired **31** by flash column chromatography (10% yield). After *N*-methylation (NaH, MeI, DMF, 87%), the benzyl group was removed under hydrogenolysis (H_2, 20% Pd/C, 87%) to give primary alcohol **33**. Two-step oxidation of alcohol **33** to the corresponding carboxylic acid (1. Parikh−Doering oxidation;[23] 2. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene), followed by esterification with trimethylsilyldiazomethane, furnished the desired methyl ester **15** in 63% yield for the three steps. Thus, the key intermediate **15** was prepared in 15 linear steps from diacetyl-L-arabinal (**6**) and 10% overall yield.

SCHEME 8. Total Synthesis of Dysiherbaine (1)



Total Synthesis of Dysiherbaine. Completion of the total synthesis of dysiherbaine required introduction of an amino acid side chain and global deprotection. Thus, the TBS group in **15** was removed with TBAF to afford primary alcohol **34** in 84% yield (Scheme 8). The stereochemistry of the C8 and C9 positions was established at this stage by NOEs as shown in Figure 2. Oxidation of **34** under Parikh−Doering conditions (SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2), followed by Horner−Wadsworth−Emmons (HWE) olefination with phosphonate **35**[24] and tetramethylguanidine, led to enamide ester **36** in 73% yield

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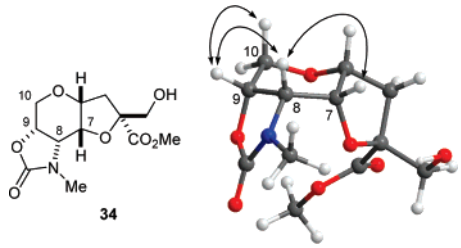


FIGURE 2. Key NOEs for stereochemical confirmation of compound **34**.

for the two steps. Subsequent asymmetric hydrogenation of **36** in the presence of 5 mol % of [Rh(I)(COD)-(*S*,*S*)-Et-DuPHOS]$^{+}$OTf^{-} catalyst[25,26] in THF under pressurized hydrogen (0.9 MPa) at room temperature proceeded cleanly to afford the desired amino acid derivative **37** in 83% yield and with greater than 20:1 diastereoselectivity. The corresponding diastereomer could not be detected in the 500 MHz ^{1}H NMR spectra. The stereochemistry of the newly generated stereocenter at C2 was tentatively assigned on the basis of Burk's empirical rule[25] and our earlier results on the total synthesis of neodysiherbaine A.[10d] Finally, global deprotection of **37** under alkaline hydrolysis conditions (40% NaOH, MeOH, 45 °C) furnished dysiherbaine (**1**) in 84% yield. The synthetic dysiherbaine was identical with the natural material as judged by the ^{1}H and ^{13}C NMR spectra. Moreover, the in vivo toxicity to mice of the intracerebroventricularly injected synthetic compound was similar to that observed for the natural sample. Thus, a concise synthesis of dysiherbaine (**1**) has been accomplished in 20 linear steps from diacetyl-L-arabinal (**6**) and 4.4% overall yield. The described synthetic route represents an improvement over that employed in our original total synthesis[9b] and allowed us to prepare sufficient quantities of dysiherbaine for biological studies.

Synthesis of Analogues. The synthetic route to dysiherbaine (**1**) developed here provided access to dysiherbaine analogues that would not have been accessible through manipulations of the natural product itself. It had been observed that neodysiherbaine A analogues with modification of the C9 hydroxy group (removal/inversion) displayed significantly reduced affinities for kainate receptors, especially GluR5 KA receptors, suggesting that the α-oriented C9 hydroxy group is a critical structural element necessary for selective binding to the GluR5 receptors. To provide a detailed understanding of SAR in this key functional group, we undertook the synthesis and biological evaluation of three C9-modified dysiherbaine analogues, i.e., 9-*epi*-dysiherbaine (**38**), 9-deoxydysiherbaine (**39**), and 9-methoxydysiherbaine (**40**), along with *N*-ethyldysiherbaine (**41**) (Figure 3).

We first synthesized 9-*epi*-dysiherabine (**38**) as summarized in Scheme 9. *N*-Methylation of **19** (NaH, MeI, DMF, 63%) was followed by TBS deprotection (TBAF, THF, 98%) to afford primary alcohol **43**. Parikh−Doering oxidation of **43** to the aldehyde and HWE reaction with phosphonate **35** generated enamide ester **44** in 79% yield for the two steps. Asymmetric

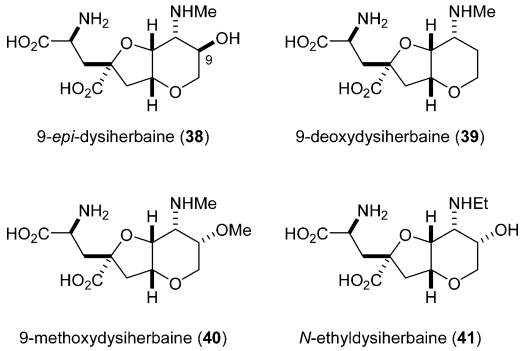
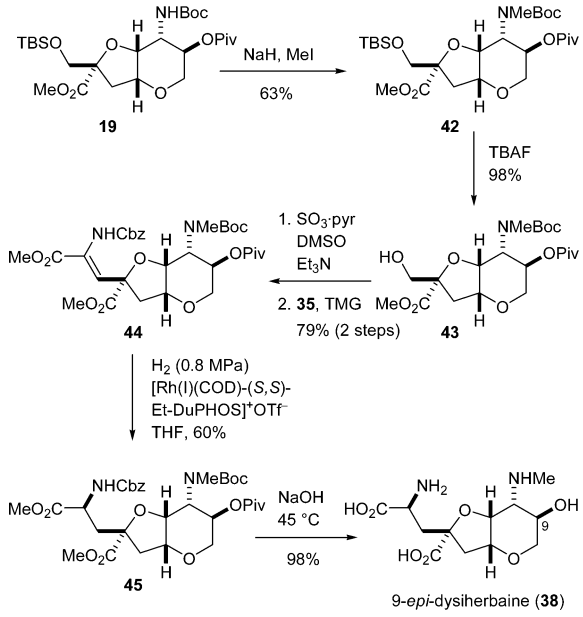


FIGURE 3. Structures of dysiherbaine analogues.

SCHEME 9. Synthesis of 9-*epi*-Dysiherbaine (38)



hydrogenation (60%) followed by global deprotection (98%) as before furnished 9-*epi*-dysiherbaine (**38**).

The synthesis of 9-deoxydysiherbaine (**39**) started with intermediate **42**, from which the pivaloyl group was removed to give **46** (NaOMe, MeOH, 83%, Scheme 10). Alcohol **46** was converted to the corresponding phenyl thiocarbonate by the action of phenyl chlorothionoformate and dimethylaminopyridine in acetonitrile (79% yield). Subsequent deoxygenation proceeded cleanly under radical conditions (Bu_3SnH, AIBN, toluene, reflux)[27,28] to deliver **47** in 79% yield. After TBS deprotection (TBAF, 83%), the resultant primary alcohol **48** was converted to 9-deoxydysiherbaine (**39**) through the same four-step sequence described above.

9-Methoxy analogue **40** was prepared starting from intermediate **23** as outlined in Scheme 11. *N*-Boc protection of the oxazolidinone under standard conditions (97%), followed by methanolysis of the cyclic carbamate group (Cs_2CO_3, MeOH, 80%), afforded *N*-Boc-amino alcohol **52**. Double-methylation of **52** (NaH, MeI, DMF) produced methyl ether **53** in 84% yield. After removal of the TBS group from **53** (TBAF, 99%), the

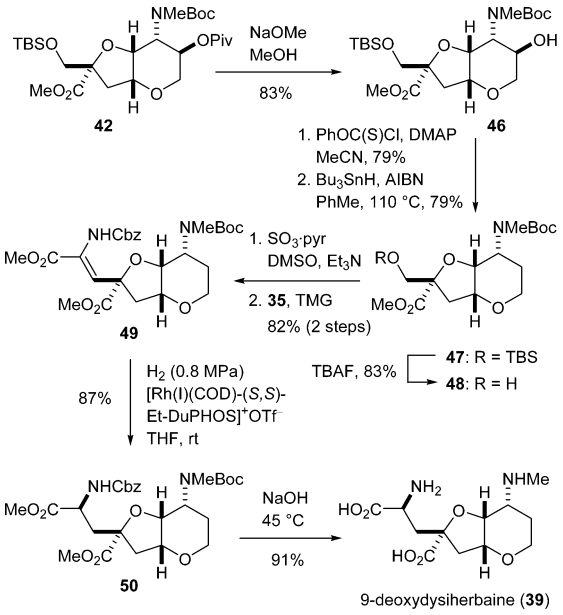
(25) (a) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363−372.

(26) (a) Debenham, S. D.; Debenham, J. S.; Burk, M. J.; Toone, E. J. *J. Am. Chem. Soc.* **1997**, *119*, 9897−9898. (b) Debenham, S. D.; Cossrow, J.; Toone, E. J. *J. Org. Chem.* **1999**, *64*, 9153−9163. (c) Allen, J. R.; Harris, C. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1890−1897. (d) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552−6554.

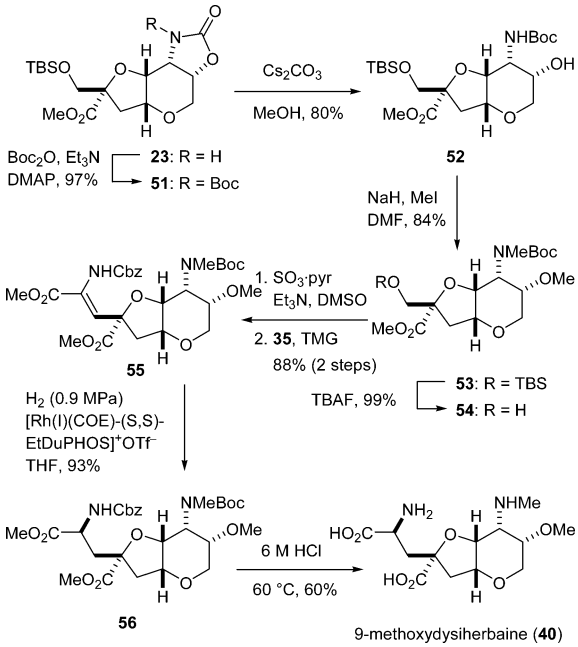
(27) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(28) (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932−933. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059−4065.

SCHEME 10. Synthesis of 9-Deoxydysiherbaine (39)



SCHEME 11. Synthesis of 9-Methoxydysiherbaine (40)



resultant primary alcohol **54** was then transformed to 9-methoxydysiherbaine (**40**) in a four-step sequence similar to that described above.

Finally, *N*-ethyl derivative **41** was synthesized from oxazolidinone **23** as summarized in Scheme 12. Treatment of **23** with iodoethane in the presence of silver(I) oxide in DMF afforded *N*-ethyl oxazolidinone **57** in 69% yield. Conversion of **57** into *N*-ethyldysiherbaine (**41**) was readily accomplished as described for the synthesis of dysiherbaine (**1**) from **15** (see Scheme 8).

Biological Studies. The in vivo toxicity of analogues **38**−**41** to mice was preliminarily investigated by intracerebroventricular injection. *N*-Ethyl derivative **41** induced noticeable convulsant activity similar to dysiherbaine (**1**), but the potency was estimated to be 10−20 times less than that of **1** (Table 1). Interestingly, injection of 9-*epi*-, 9-deoxy-, and 9-methoxydysiherbaines (**38**−**40**, respectively) also resulted in the induction

SCHEME 12. Synthesis of *N*-Ethyldysiherbaine (41)

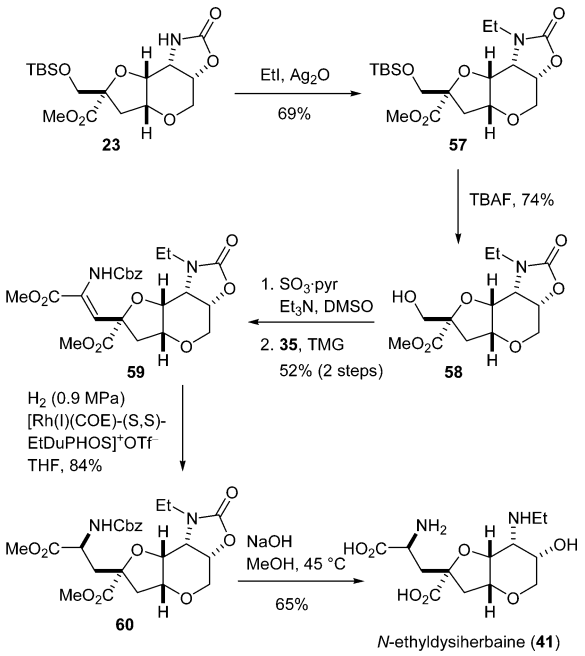


TABLE 1. Epileptogenic Activity for Natural Dysiherbaine (1) and Synthetic Analogues 38−41

entry	compd	ED_{50} (nmol/mouse)
1	DH (**1**)	0.013
2	**38**	29
3	**39**	*a*
4	**40**	7.1
5	**41**	0.16

[a] Not determined.

of seizures, but their activities were much less potent than that observed for dysiherbaine (**1**). 9-Deoxy derivative **39** induced convulsion in mice only when a very high dose of 130 μmol/mouse was given. These results suggest that the α-oriented C9 hydroxy group is an important structural element required for the convulsant potency of dysiherbaine (**1**).

The binding affinities of analogues **38**−**41** for native ionotropic glutamate receptors were next evaluated by radioligand binding assays with [^{3}H]KA, [^{3}H]AMPA, or [^{3}H]CGP 39653 (an NMDA receptor ligand) in rat brain synaptic membranes (Table 2).[5] Compounds **38** and **39**, weak convulsants in mice, did not displace any of the radioligands tested at 10 μM. Although both compounds **40** and **41** displaced [^{3}H]KA, the affinities for [^{3}H]AMPA-binding sites were lost with these modifications. The drastic loss (300-fold as compared to **1**) of **41** to displace [^{3}H]KA is of particular interest, considering the reasonable retention of the convulsant activity. Further insights into the modes of action of these compounds will be provided by our ongoing molecular pharmacological studies using individual receptor subunits of AMPA/KA receptors.

In conclusion, we have achieved a rapid and efficient total synthesis of dysiherbaine (**1**). The present synthetic approach allowed for the generation of several dysiherbaine analogues. The preliminary SAR studies of these variants revealed that the presence and stereochemistry of the C9 hydroxy group in dysiherbaine is important for high-affinity and selective binding to ionotropic glutamate receptors as was observed in the SAR

TABLE 2. Receptor-Binding Affinity of Natural Dysiherbaine (1) and Synthetic Analogues 38−41 for Native AMPA and KA Receptors[a]

		[^{3}H]AMPA binding		[^{3}H]KA binding	
entry	compd	K_i (μM) [a]	% at 10 μM[d]	K_i (μM)[a]	% at 10 μM[d]
1	DH (**1**)	0.153 ± 0.011[b]	0[e]	0.026 ± 0.004[b]	0[e]
2	**38**	>10[c]	104 ± 2	>10[c]	90 ± 7
3	**39**	>10[c]	109 ± 13	>10[c]	94 ± 5
4	**40**	>10[c]	77 ± 5	9.3 ± 1.8	54 ± 3
5	**41**	>10[c]	86 ± 9	8.2 ± 2.3	51 ± 1

[a] K_i values were determined from IC_{50} values in the displacement of [^{3}H]ligand binding from rat synaptic membranes. [b] K_i values for DH taken from ref 5. [c] K_i values were not determined as it is larger than 10 μM. [d] Values of the specific binding in the presence of the compound (10 μM) are presented as % against control. [e] Specific binding of radioligand was completely displaced by 10 μM of the compound.

studies for neodysiherbaine A analogues.[10d] In contrast to nearly complete loss of activity in 9-deoxy analogue **39**, activities for 9-methoxy derivative **40** were retained in some extent. This suggests that an electron negative atom at the C9α position would be one of the key determinants for the receptor interaction. Interestingly epileptogenic activity for *N*-ethyl analogue **41** was potent for its affinity to the [^{3}H]KA binding site. This may indicate that the modification caused a shift in receptor selectivity to subtype receptor proteins that are not largely expressed in the cortical synaptic population but are responsible for epileptogenic activity in mice.

Experimental Section

Alcohol 24. To a solution of acetate **8** (5.61 g, 28.6 mmol) in methanol (100 mL) at room temperature was added K_2CO_3 (2.57 g, 18.6 mmol). The resulting solution was stirred at room temperature for 30 min before it was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with water (100 mL) and brine (60 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 50% ethyl acetate/hexanes) afforded alcohol **24** (4.47 g, 92%) as a colorless oil: $[\alpha]^{28}_D$ −77.5 (*c* 0.45, $CHCl_3$); IR (film) 3394, 2917, 2360, 1698, 1652, 1540, 1521, 1456, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.87 (d, J = 10.0 Hz, 1H), 5.80 (d, J = 10.0 Hz, 1H), 5.16 (s, 1H), 5.03 (s, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.27−4.25 (m, 1H), 4.13 (br s, 1H), 4.02 (d, J = 11.0 Hz, 1H), 4.02 (d, J = 12.5 Hz, 1H), 3.97 (d, J = 12.5 Hz, 1H), 3.42 (dd, J = 11.0, 6.5 Hz, 1H), 2.36 (dd, J = 14.5, 9.0 Hz, 1H), 2.27 (dd, J = 14.5, 5.5 Hz, 1H), 1.60 (d, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 138.3, 132.1, 128.4 (×2), 128.3 (×2), 127.8, 127.7, 114.9, 72.9, 72.0, 71.9, 68.2, 62.6, 37.7; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{20}O_3Na$ [(M + Na)$^+$] 283.1310, found 283.1305.

Alcohol 25. To a solution of alcohol **24** (4.47 g, 17.2 mmol), triphenylphosphine (6.80 g, 25.8 mmol), and diethyl azodicarboxylate (2.2 M in toluene, 11.7 mL, 25.8 mmol) in THF (170 mL) at 0 °C was added acetic acid (1.47 mL, 25.8 mmol). The resultant solution was stirred at room temperature for 17 h before it was poured into saturated aqueous $NaHCO_3$ (200 mL). The mixture was extracted with ethyl acetate (2 × 200 mL), and the combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ethyl acetate/hexanes) afforded acetate (5.04 g, 97%) as a colorless oil: $[\alpha]^{28}_D$ +91.1 (*c* 1.74, $CHCl_3$); IR (film) 3396, 2850, 1733, 1652, 1541, 1507, 1455, 1371, 1239, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 6.00 (d, J = 10.0 Hz, 1H), 5.91−5.88 (m, 1H), 5.18 (s, 1H), 5.06 (s, 1H), 4.97 (br s, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.17 (dd, J = 8.0, 6.0 Hz, 1H), 4.03 (d, J = 12.5 Hz, 1H), 4.03 (d, J = 13.0 Hz, 1H), 3.98 (d, J = 13.0 Hz, 1H), 3.71 (dd, J = 12.5, 2.5 Hz, 1H), 2.44 (dd, J = 14.5, 8.0 Hz, 1H), 2.35 (dd, J = 14.5, 6.0 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 141.9, 138.5, 135.9, 128.4 (×2), 127.6 (×3), 122.4, 115.0, 73.0, 72.3, 72.0, 67.9, 64.6, 38.6, 21.2; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{22}O_4Na$ [(M + Na)$^+$] 325.1416, found 325.1395.

To a solution of the above acetate (5.04 g, 16.7 mmol) in methanol (100 mL) at room temperature was added K_2CO_3 (2.31 g, 16.7 mmol). The resulting solution was stirred at room temperature for 30 min before it was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with water (100 mL) and brine (60 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 40% ethyl acetate/hexanes) afforded alcohol **25** (4.22 g, 97%) as a colorless oil: $[\alpha]^{28}_D$ +55.0 (*c* 0.62, $CHCl_3$); IR (film) 3397, 2917, 1652, 1541, 1456, 1385, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5H), 5.99−5.96 (m, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.18 (s, 1H), 5.05 (s, 1H), 4.48 (s, 2H), 4.17 (dd, J = 7.0, 6.0 Hz, 1H), 4.02 (d, J = 12.5 Hz, 1H), 4.00 (d, J = 10.0 Hz, 1H), 3.95 (d, J = 10.0 Hz, 1H), 3.84 (br s, 1H), 3.65 (d, J = 12.5 Hz, 1H), 2.38 (dd, J = 14.5, 7.5 Hz, 1H), 2.33 (dd, J = 14.5, 6.0 Hz, 1H), 1.90 (d, J = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 138.2, 133.5, 128.5 (×2), 127.8 (×2), 127.6, 126.8, 115.0, 72.9, 72.7, 71.8, 70.3, 62.3, 38.6; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{20}O_3Na$ [(M + Na)$^+$] 283.1310, found 283.1300.

***N*-Benzoyl Oxazolidinone 27.** To a solution of alcohol **25** (3.49 g, 13.4 mmol) in THF (50 mL) at room temperature was added benzoyl isocyanate (1.85 mL, 14.7 mmol). The resultant solution was stirred at room temperature for 14 h before it was concentrated under reduced pressure. The crude *N*-benzoyl carbamate **26** thus obtained was used in the next reaction without purification.

To a solution of sodium iodide (6.03 g, 40.2 mmol) and *tert*-butyl hypochlorite (4.55 mL, 40.2 mmol) in acetonitrile (90 mL) at room temperature was added the above *N*-benzoyl carbamate **26** in acetonitrile (40 mL). The resulting solution was stirred at room temperature for 19 h before it was quenched with saturated aqueous Na_2SO_3 (100 mL). The mixture was extracted with ethyl acetate (500 mL). The aqueous layer was separated and extracted with ethyl acetate (100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ethyl acetate/hexanes) afforded *N*-benzoyl oxazolidinone **27** (6.14 g, 86% for the two steps) as a white solid: $[\alpha]^{28}_D$ +114.7 (*c* 0.45, $CHCl_3$); IR (film) 3388, 2917, 1790, 1686, 1384, 1700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.0 Hz, 2H), 7.56 (dd, J = 7.0, 7.0 Hz, 1H), 7.24 (dd, J = 8.0, 8.0 Hz, 2H), 7.36−7.26 (m, 5H), 5.28 (dd, J = 6.0, 6.0 Hz, 1H), 5.16, (s, 1H), 4.98 (s, 1H), 4.61 (dd, J = 8.0, 2.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.33 (dd, J = 6.0, 6.0 Hz, 1H), 4.31 (d, J = 13.0 Hz, 1H), 4.19 (ddd, J = 8.0, 6.0, 6.0 Hz, 1H), 3.99 (dd, J = 13.0, 2.0 Hz, 1H), 3.96 (s, 2H), 2.64 (dd, J = 14.5, 5.0 Hz, 1H), 2.37 (dd, J = 14.5, 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 152.7, 141.2 138.2, 133.2, 132.3, 129.8 (×2), 128.5 (×2), 128.1 (×2), 127.9 (×2), 127.7, 116.0, 79.7, 72.8, 72.7, 72.0, 65.9, 59.2, 40.1, 23.6; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{24}NO_5INa$ [(M + Na)$^+$] 556.0597, found 556.0582.

Oxazolidinone 28. To a solution of *N*-benzoyl oxazolidinone **27** (6.12 g, 11.5 mmol) and methanol (1.9 mL, 46.0 mmol) in THF

(115 mL) at 0 °C was added $LiBH_4$ (1.00 g, 46.0 mmol). The resulting solution was stirred at 0 °C for 10 min before it was quenched with saturated aqueous potassium sodium tartrate (50 mL). The mixture was stirred at 0 °C for 1 h and extracted with ethyl acetate (2 × 300 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 50% ethyl acetate/hexanes) afforded oxazolidinone **28** (3.16 g, 64%) as a white foam: $[\alpha]^{28}_D$ −22.8 (*c* 0.89, $CHCl_3$); IR (film) 3302, 2917, 2850, 1756, 1384, 1219, 1128, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.65 (s, 1H), 5.19 (s, 1H), 5.07 (s, 1H), 4.52 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 14.5 Hz, 1H), 4.28 (dd, J = 6.5, 2.0 Hz, 1H), 4.13 (dd, J = 9.0, 6.0 Hz, 1H), 4.02 (d, J = 12.0 Hz, 1H), 3.96 (d, J = 12.0 Hz, 1H), 3.71 (dd, J = 10.5, 9.0 Hz, 1H), 3.65 (dd, J = 14.5, 2.5 Hz, 1H), 3.53 (ddd, J = 10.5, 9.0, 2.5 Hz, 1H), 2.92 (d, J = 14.5 Hz, 1H), 2.22 (dd, J = 14.5, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 141.7, 138.3, 128.4 (×2), 127.8 (×2), 127.7, 115.6, 77.1, 74.9, 72.9, 71.9, 66.5, 61.0, 38.4, 34.8; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}NO_4INa$ [$(M + Na)^+$] 452.0335, found 452.0307.

Diol 29. To a solution of OsO_4 (1% solution in *tert*-butanol, 313 μL, 0.0123 mmol), $(DHQD)_2AQN$ (21.1 mg, 0.0246 mmol), K_2CO_3 (102 mg, 0.738 mmol), and $K_2[Fe(CN)_6]$ (243 mg, 0.738 mmol) in water (2.5 mL) at 0 °C were added a solution of oxazolidinone **28** (106 mg, 0.246 mmol) in *tert*-butanol (2.5 mL) and methanesulfonamide (46.8 mg, 0.492 mmol). The resulting mixture was stirred at room temperature for 17.5 h before it was quenched with saturated aqueous Na_2SO_3 (5 mL). The resulting mixture was stirred at room temperature for an additional 30 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 3% methanol/$CHCl_3$) afforded diol **29** (101 mg, 88%) as an inseparable 4.8:1 mixture of diastereomers as a colorless oil: $[\alpha]^{28}_D$ −28.2 (*c* 0.44, $CHCl_3$); IR (film) 3387, 2918, 1752, 1384, 1071 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (major diastereomer) 7.37−7.28 (m, 5H), 5.67 (br s, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.31 (d, J = 14.0 Hz, 1H), 4.24 (dd, J = 6.5, 2.0 Hz, 1H), 4.06 (dd, J = 9.5, 6.5 Hz, 1H), 3.67 (dd, J = 10.0, 9.5 Hz, 1H), 3.59 (dd, J = 10.0, 1.5 Hz, 1H), 3.55−3.51 (m, 3H), 3.44 (d, J = 9.5 Hz, 1H), 3.40 (d, J = 9.5 Hz, 1H), 3.28 (s, 1H), 2.39 (dd, J = 15.0, 1.5 Hz, 1H), 2.32 (dd, J = 7.0, 7.0 Hz, 1H), 1.57 (dd, J = 15.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major diastereomer) 158.5, 137.6, 128.4 (×2), 128.3 (×2), 127.9, 75.7, 74.6, 73.4, 72.7, 65.6, 66.1, 60.5, 43.3, 38.2, 34.6; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}NO_6INa$ [$(M + Na)^+$] 486.0390, found 486.0390.

TBS Ether 30. To a solution of diol **29** (51.6 mg, 0.111 mmol), triethylamine (52 μL, 0.37 mmol), and DMAP (2.72 mg, 0.0222 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added TBSCl (27.4 mg, 0.133 mmol). The resulting solution was allowed to warm to 35 °C and stirred at the same temperature for 37 h. The mixture was extracted with ethyl acetate (20 mL), then washed with water (5 mL), 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. Flash column chromatography (silica gel, 40% ethyl acetate/hexanes) afforded TBS ether **30** (54.0 mg, 84%) as an inseparable 4.8:1 mixture of diastereomers, as a white foam: $[\alpha]^{28}_D$ −17.8 (*c* 1.17, $CHCl_3$); IR (film) 3303, 2924, 2853, 1755, 1384, 1250, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (major diastereomer) 7.34−7.25 (m, 5H), 5.59 (br s, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.28 (d, J = 15.0 Hz, 1H), 4.23 (dd, J = 6.5, 2.0 Hz, 1H), 4.08 (dd, J = 7.0, 7.0 Hz, 1H), 3.68, (d, J = 15.0 Hz, 1H), 3.68 (dd, J = 8.0, 7.5 Hz, 1H), 3.55 (dd, J = 14.0, 2.5 Hz, 1H), 3.54 (s, 2H), 3.45 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 3.08 (s, 1H), 2.37 (dd, J = 15.5, 1.5 Hz, 1H), 1.62 (dd, J = 15.5, 7.5 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major diastereomer) 158.0, 138.0, 128.4, 128.3, 128.1 (×2), 127.2, 75.7, 74.7, 73.5, 73.4, 72.8, 66.5, 66.0, 60.9, 38.8, 35.7, 25.9 (×3), 18.3, −5.5 (×2); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{36}NO_6SiINa$ [$(M + Na)^+$] 600.1254, found 600.1233.

Bicyclic Ether 31. A solution of TBS ether **30** (41.9 mg, 0.0726 mmol) in pyridine (2 mL) was heated at reflux for 24 h. The resulting solution was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), washed with aqueous 1 M HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 50% ethyl acetate/hexanes) afforded bicyclic ether **31** (22.9 mg, 70%) along with the C4 diastereomer (3.2 mg, 10%) as a white foam, respectively. **31**: $[\alpha]^{28}_D$ +11.4 (*c* 1.49, $CHCl_3$); IR (film) 3348, 2928, 2855, 1754, 1470, 1383, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 6.36 (s, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.56 (dd, J = 10.0, 1.0 Hz, 1H), 4.52 (dd, J = 14.0, 7.0 Hz, 1H), 4.29 (dd, J = 9.0, 5.0 Hz, 1H), 4.09 (dd, J = 6.0, 5.5 Hz, 1H), 3.98 (d, J = 14.0 Hz, 1H), 3.51 (d, J = 10.0 Hz, 1H), 3.42 (d, J = 10.0 Hz, 1H), 3.90 (d, J = 10.0 Hz, 1H), 3.88 (d, J = 10.0 Hz, 1H), 3.36 (dd, J = 14.0, 2.0 Hz, 1H), 2.26 (dd, J = 13.0, 8.0 Hz, 1H), 2.20 (dd, J = 13.0, 7.0 Hz, 1H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 137.2, 128.5 (×2), 128.1 (×2), 127.9, 85.6, 77.9, 73.9, 73.5, 72.1, 71.2, 67.4, 66.8, 51.4, 36.3, 25.8 (×3), 18.2, −5.6 (×2); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{35}NO_6SiNa$ [$(M + Na)^+$] 472.2131, found 472.2116. **C4 diastereomer**: $[\alpha]^{28}_D$ −0.45 (*c* 1.05, $CHCl_3$); IR (film) 3280, 2927, 2855, 1757, 1470, 1384, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 6.00 (s, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 14.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.45 (dd, J = 14.0, 7.0 Hz, 1H), 4.24 (dd, J = 9.0, 5.0 Hz, 1H), 4.09 (dd, J = 5.5, 5.5 Hz, 1H), 3.99 (d, J = 14.0 Hz, 1H), 3.71 (d, J = 10.0 Hz, 1H), 3.59 (d, J = 10.0 Hz, 1H), 3.38 (dd, J = 14.0, 2.0 Hz, 1H), 3.33 (d, J = 10.0 Hz, 1H), 3.31 (d, J = 10.0 Hz, 1H), 2.25 (dd, J = 13.0, 7.0 Hz, 1H), 2.21 (dd, J = 13.0, 7.0 Hz, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 138.1, 128.5 (×2), 127.8 (×2), 127.5, 85.1, 77.7, 73.9, 73.6, 73.5, 71.8, 66.6, 65.4, 51.1, 36.1, 25.9 (×3), 18.5, −5.6 (×2); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{35}NO_6SiNa$ [$(M + Na)^+$] 472.2131, found 472.2115.

***N*-Methyl Oxazolidinone 32.** To a solution of oxazolidinone **31** (68.6 mg, 0.153 mmol) in DMF (1.5 mL) at 0 °C was added sodium hydride (oil free, 11.0 mg, 0.458 mmol). After being stirred at 0 °C for 30 min, the reaction mixture was treated with iodomethane (29 μL, 0.47 mmol). The resulting solution was allowed to warm to room temperature and stirred for 17 h. Saturated aqueous NH_4Cl (3 mL) was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 40% ethyl acetate/hexanes) afforded *N*-methyl oxazolidinone **32** (61.5 mg, 87%) as a white foam: $[\alpha]^{28}_D$ +17.1 (*c* 1.11, $CHCl_3$); IR (film) 3398, 2927, 2855, 1755, 1432, 1094, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.22 (m, 5H), 4.50 (d, J = 13.0 Hz, 1H), 4.48 (d, J = 13.0 Hz, 1H), 4.25 (d, J = 6.5 Hz, 1H), 4.21 (d, J = 13.5 Hz, 1H), 4.12 (d, J = 5.5, 1H), 3.97 (d, J = 4.0 Hz, 1H), 3.70 (dd, J = 6.5, 5.5 Hz, 1H), 3.64 (d, J = 11.0 Hz, 1H), 3.61 (d, J = 11.0 Hz, 1H), 3.58 (d, J = 10.0 Hz, 1H), 3.53 (dd, J = 13.5, 1.5 Hz, 1H), 3.45 (d, J = 10.0 Hz, 1H), 2.91 (s, 3H), 2.35 (dd, J = 14.0, 5.0 Hz, 1H), 2.07 (d, J = 14.0 Hz, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 138.7, 128.2 (×2), 127.5 (×2), 127.3, 84.3, 76.9, 74.0, 73.6, 73.5, 68.9, 66.8, 64.1, 54.9, 36.5, 30.0, 25.8 (×3), 18.1, −5.5 (×2); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{37}NO_6SiNa$ [$(M + Na)^+$] 486.2288, found 486.2268.

Alcohol 33. A suspension of *N*-methyl oxazolidinone **32** (61.5 mg, 0.133 mmol) and 20% Pd/C (1.5 g) in ethyl acetate (1.3 mL) was stirred at room temperature under hydrogen atmosphere for 4 h. The mixture was filtered through a pad of Celite, and the filtrate

was concentrated under reduced pressure. Flash column chromatography (silica gel, 1% ethyl acetate/hexanes) afforded alcohol **33** (43.3 g, 87%) as a white foam: $[\alpha]^{28}_D + 0.02$ (*c* 0.43, $CHCl_3$); IR (film) 3457, 2925, 2855, 1734, 1434, 1068, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.26 (d, $J = 14.0$ Hz, 1H), 4.24 (dd, $J = 6.0$, 2.0 Hz, 1H), 4.11 (dd, $J = 6.0$, 2.0 Hz, 1H), 3.95 (dd, $J = 5.0$, 2.0 Hz, 1H), 3.71 (dd, $J = 6.0$, 6.0 Hz, 1H), 3.61 (d, $J = 9.5$ Hz, 1H), 3.58 (dd, $J = 11.0$, 4.0 Hz, 1H), 3.54 (dd, $J = 14.0$, 2.0 Hz, 1H), 3.48 (d, $J = 9.5$ Hz, 1H), 3.46 (dd, $J = 11.0$, 4.5 Hz, 1H), 2.90 (s, 3H), 2.34 (dd, $J = 14.0$, 5.0 Hz, 1H), 2.27 (br s, 1H), 2.00 (d, $J = 14.0$ Hz, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 85.0, 76.7, 74.1, 69.0, 66.0, 65.6, 64.1, 54.8, 36.6, 30.0, 25.7 (×3), 18.1, −5.6 (×2); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{31}NO_6SiNa$ $[(M + Na)^+]$ 396.1818, found 396.1823.

Methyl Ester 15. To a solution of alcohol **33** (8.0 mg, 0.0214 mmol) in CH_2Cl_2/DMSO (4/1, v/v, 1.0 mL) at 0 °C were added triethylamine (14.9 μL, 0.107 mmol) and SO_3·pyridine (13.6 mg, 0.0856 mmol). The resultant mixture was stirred at room temperature for 4 h. The reaction mixture was extracted with $CHCl_3$ (3 × 10 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 colorless oil, which was used in the next reaction without purification.

To a solution of the above aldehyde in *tert*-butanol/water (4/1, v/v, 1.0 mL) at 0 °C were added 2-methyl-2-butene (200 μL), NaH_2PO_4 (5.1 mg, 0.043 mmol), and $NaClO_2$ (9.7 mg, 0.11 mmol). The resulting mixture was stirred at room temperature for 2 h before it was poured into $CHCl_3$/water (3:1, v/v, 10 mL). The mixture was acidified to pH 2 with aqueous 1 M HCl, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (5 × 5 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, which was used in the next reaction without purification.

To a solution of the above carboxylic acid in methanol/benzene (1:1, v/v, 1.0 mL) at room temperature was added $TMSCHN_2$ (2 M in diethyl ether, 21.4 μL, 0.0428 mmol). The resulting solution was stirred at room temperature for 10 min before it was concentrated under reduced pressure. Flash column chromatography (silica gel, 1% methanol/$CHCl_3$) afforded methyl ester **15** (5.4 mg, 63% for the three steps) as a white foam: $[\alpha]^{19}_D = +27.1$ (*c* 0.64, $CHCl_3$); IR (film) 2952, 2929, 2857, 1752, 1436, 1256, 1227, 1131, 1094, 1031, 840, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCL_3$) δ 4.24 (ddd, $J = 7.2$, 2.1, 1.8 Hz, 1H), 4.18 (brd, $J = 13.8$ Hz, 1H), 4.08 (dd, $J = 5.7$, 2.1 Hz, 1H), 3.93 (m, 1H), 3.79 (d, $J = 10.5$ Hz, 1H), 3.73 (dd, $J = 6.9$, 5.7 Hz, 1H), 3.70 (s, 3H), 3.64 (d, $J = 10.5$ Hz, 1H), 3.49 (dd, $J = 13.8$, 2.1 Hz, 1H), 2.96 (s, 3H), 2.56 (brd, $J = 13.5$ Hz, 1H), 2.50 (dd, $J = 13.5$, 3.6 Hz, 1H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 159.2, 86.8, 75.8, 74.9, 68.4, 65.6, 64.2, 54.5, 52.1, 38.2, 29.9, 25.5 (×3), 17.9, −5.7, −5.8; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{31}NO_7SiNa$ $[(M + Na)^+]$ 424.1767, found 424.1775.

Alcohol 34. To a solution of *N*-methyl oxazolidinone **15** (198.6 mg, 0.495 mmol) in THF (5.0 mL) at 0 °C was added TBAF (1.0 M in THF, 0.74 mL, 0.74 mmol). The resulting solution was stirred at room temperature for 20 min before it was concentrated under reduced pressure. Flash column chromatography (silica gel, 2% methanol/$CHCl_3$) afforded alcohol **34** (119.3 mg, 84%) as a white form: $[\alpha]^{18}_D$ +69.1 (*c* 1.11, $CHCl_3$); IR (film) 3326 (br), 2911, 1741, 1441, 1225, 1130, 1066 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.27 (d, $J = 6.7$ Hz, 1H), 4.22 (d, $J = 13.8$ Hz, 1H), 4.14 (dd, $J = 5.6$, 2.1 Hz, 1H), 3.96 (br s, 1H), 3.79 (dd, $J = 6.7$, 6.2 Hz, 1H), 3.77 (d, $J = 11.4$ Hz, 1H), 3.73 (s, 3H), 3.63 (d, $J = 11.4$ Hz, 1H), 3.51 (dd, $J = 13.8$, 2.1 Hz, 1H), 2.98 (s, 3H), 2.66 (d, $J = 13.5$ Hz, 1H), 2.31 (dd, $J = 13.5$, 3.8 Hz, 1H), 2.16 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 159.1, 86.3, 75.3, 74.6, 68.3, 65.5, 64.0, 54.2, 52.0, 38.9, 29.8; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{17}NO_7SiNa$ $[(M + Na)^+]$ 310.0903, found 310.0889.

Enamide Ester 36. To a solution of alcohol **34** (119.3 mg, 0.415 mmol) in CH_2Cl_2/DMSO (4:1, v/v, 5.0 mL) at 0 °C were added triethylamine (289 μL, 2.08 mmol) and SO_3·pyridine (231 mg, 1.66 mmol). The resulting mixture was stirred at room temperature for 1 h before pH 7.0 phosphate buffer (2.0 mL) was added. The mixture was carefully extracted with $CHCl_3$ (20 × 20 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude aldehyde (246.0 mg) as a colorless oil, which was used in the next reaction without purification.

To a solution of the above aldehyde in CH_2Cl_2 (4.0 mL) at 0 °C were added $(MeO)_2P(O)CH(NHCbz)CO_2Me$ **35** (412 mg, 1.25 mmol) and tetramethylguanidine (208 μL, 1.66 mmol). The resulting solution was stirred at room temperature for 1 h before saturated aqueous NH_4Cl (2 mL) was added. The mixture was extracted with $CHCl_3$ (5 × 10 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 70% ethyl acetate/hexanes) afforded enamide ester **36** (149.4 mg, 73% for the two steps) as a pale yellow oil: $[\alpha]^{18}_D$ +13.3 (*c* 0.80, $CHCl_3$); IR (film) 3377, 2952, 1733, 1654, 1487, 1437, 1281, 1225, 1133, 1063, 1029, 766, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.40−7.25 (m, 5H), 6.07 (s, 1H), 5.12 (s, 2H), 4.22 (br d, $J = 6.9$ Hz, 1H), 4.16 (d, $J = 14.1$ Hz, 1H), 4.12 (dd, $J = 5.4$, 2.1 Hz, 1H), 3.89 (m, 1H), 3.75 (m, 1H), 3.70 (s, 6H), 3.47 (dd, $J = 13.8$, 2.1 Hz, 1H), 3.12 (d, $J = 13.5$ Hz, 1H), 2.88 (s, 3H), 2.19 (dd, $J = 13.5$, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 164.2, 158.5, 153.4, 135.6, 130.2, 128.3 (×2), 128.1, 128.0 (×2), 126.0, 84.1, 74.7, 74.2, 68.0, 67.2, 64.2, 53.9, 52.9, 52.3, 43.7, 29.6; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{26}N_2O_{10}Na$ $[(M + Na)^+]$ 513.1485, found 513.1496.

Protected Dysiherbaine 37. A degassed mixture of enamide ester **36** (149.4 mg, 0.305 mmol) and [Rh(I)(COD)-(*S*,*S*)-Et-DuPHOS]$^+$OTf$^-$ (11 mg, 0.015 mmol) in freshly distilled THF (1.5 mL) was placed in a hydrogenation bottle and pressurized with hydrogen to an initial pressure of 0.9 MPa. The resulting solution was stirred at room temperature for 88 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, 70% ethyl acetate/hexanes) afforded protected dysiherbaine **37** (124.1 mg, 83%) as a pale yellow oil: $[\alpha]^{19}_D$ +11.5 (*c* 1.12, $CHCl_3$); IR (film) 3337, 2952, 1748, 1522, 1437, 1269, 1226, 1135, 1029, 899, 856, 764, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 5.62 (d, $J = 7.2$ Hz, 1H), 5.09 (s, 2H), 4.34 (m, 1H), 4.23 (br d, $J = 6.6$ Hz, 1H), 4.17 (d, $J = 14.4$ Hz, 1H), 4.13 (br d, $J = 4.8$ Hz, 1H), 3.86 (br s, 1H), 3.76 (dd, $J = 6.6$, 6.6 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.45 (dd, $J = 14.4$, 1.5 Hz, 1H), 2.92 (s, 3H), 2.81 (d, $J = 13.8$ Hz, 1H), 2.43 (dd, $J = 15.0$, 4.5 Hz, 1H), 2.13 (dd, $J = 13.8$, 3.0 Hz, 1H), 2.09 (dd, $J = 15.0$, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7, 171.9, 158.5, 155.8, 136.2, 128.4 (×2), 128.0 (×3), 84.7, 75.3, 74.7, 68.2, 67.0, 64.6, 54.2, 52.5 (×2), 51.1, 43.5, 39.0, 30.1; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{28}N_2O_{10}Na$ $[(M + Na)^+]$ 515.1642, found 515.1623.

Dysiherbaine (1). To a solution of protected dysiherbaine **37** (40.9 mg, 0.0830 mmol) in methanol (0.5 mL) at room temperature was added aqueous 40% NaOH (0.5 mL). The resulting solution was stirred at 45 °C for 14 h before it was acidified with aqueous 1 M HCl (2 mL). The mixture was subjected to ion-exchange chromatography (Amberlite IRC76, H_2O; Dowex 50W, H_2O then 4% NH_4OH) and lyophilization to give dysiherbaine (**1**) (21.3 mg, 84%) as a white foam: $[\alpha]^{21}_D$ +4.3 (*c* 0.15, H_2O); IR (KBr) 3419, 3400−2500 (br), 1604, 1506, 1111 cm^{-1}; ^1H NMR (500 MHz, D_2O) 4.30 (br s, 1H), 4.15 (br s, 1H), 3.87 (d, $J = 14.5$ Hz, 1H), 3.84 (br s, 1H), 3.54 (s, 1H), 3.53 (d, $J = 12.5$ Hz, 1H), 3.48 (br d, $J = 11.5$ Hz, 1H), 2.74 (s, 3H), 2.59 (br d, $J = 15.0$ Hz, 1H), 2.57 (d, $J = 13.5$ Hz, 1H), 2.15 (dd, $J = 13.5$, 3.0 Hz, 1H), 1.92 (dd, $J = 15.0$, 11.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 181.8, 175.4, 90.2, 77.8, 76.5, 70.3, 63.8, 58.1, 55.2, 46.0, 40.9, 31.2; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{19}N_2O_7$ $[(M - H)^-]$ 303.1192, found 303.1174.

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Supporting Information Available: General experimental methods and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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