Total Synthesis of Dysiherbaine

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A convergent total synthesis of the marine natural product dysiherbaine was accomplished. The key steps of the synthesis are an alkylation at the γ-carbon of a protected glutamate with a highly substituted pyran derived from mannose, which was followed by a ring-contraction cascade reaction, which simultaneously gave the tetrasubstituted carbon and the hexahydrofuro[3,2-*b*]pyran ring system of the natural product.

Introduction

Advances in the study of the mammalian central nervous system (CNS) have been highly dependent on the design, synthesis, and discovery of new pharmacological probes.[1−3] For example, the excitatory amino acid (EAA) l-glutamate, the principle excitatory neurotransmitter in the mammalian CNS, is known to bind to a number of receptors that have been pharmacologically differentiated by their interaction with selective agonists and antagonists.[4] In addition, our group[5] and others[6−8] have reported the discovery of a number of conformationally constrained glutamate analogues that bind selectively to specific subclasses of EAA receptors and transporters. There are also a number of glutamate-like natural products, such as the kainoids, that are among the most selective glutamate receptor agonists known. The availability of these selective probes has contributed to the identification/differentiation of five major subclasses of glutamate receptors: kainic acid (KA), DL-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), (1*R*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD), and (*S*)-2-amino-4-phosphonobutyric acid (AP-4) receptors (Figure 1).[4]

The KA, AMPA, and NMDA receptors are ionotropic glutamate receptors (iGluRs) that mediate fast excitatory synaptic transmission in the CNS, whereas the ACPD and AP-4 receptors are metabotropic glutamate receptors (mGluRs) that mediate neuronal signaling processes in the CNS. The result of glutamate binding to iGlurRs is ion channel opening, the influx of Na^+ and Ca^{2+}, and the efflux of K^+. Normally, this process leads to cell depolarization, neurotransmission, and intracellular signaling;[4] however, when it is not properly regulated, the result is neuronal overactivation and eventually cell death. This phenomenon, known as glutamate excitotoxicity, is a common final pathway of such conditions as Huntington's disease, stroke, hypoglycemia, Alzheimer's disease, ALS, and multiple sclerosis.[9−16] Glutamate receptor antagonists have been shown to ameliorate the symptoms of excitotoxicity, implying that antagonists are potential neuroprotectants.[15,16] More generally, the discovery of new selective glutamate receptor agonists, antagonists, and neuromodulators will further advance the mechanistic understanding of these receptors, which in turn may lead to therapeutic intervention for diseases involving dysfunctional glutamate receptors.[1−3,5−8]

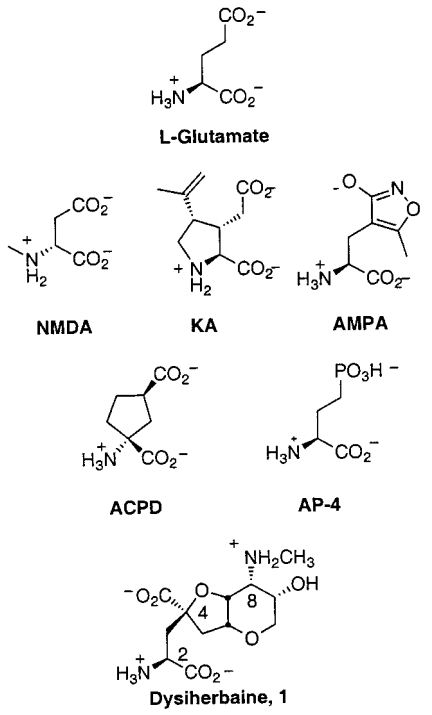

Figure 1. Partial list of glutamate receptor agonists.

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A truly novel agonist, dysiherbaine, was isolated from extracts of the Micronesian sponge *Dysidea herbacea* and its structure reported in 1997 by Sakai and co-workers. This natural product binds specifically to the KA and AMPA glutamate receptor subtypes (IC_{50} = 26 and 153 nM for the KA and AMPA receptors, respectively) and has been shown not to bind to NMDA glutamate receptor subtypes (IC_{50} > 10000 nM).[17,18] Dysiherbaine is particularly interesting as a lead compound for the discovery of new iGluR agonists and antagonists because the substitution pattern of the embedded glutamate moiety differs dramatically from that of other known EAA ligands. Because the structure is so dissimilar to that of previously known iGluR ligands, it is likely that the bicyclic ring system makes contacts in the binding sites of the KA and AMPA receptors that other agonists do not; thus, dysiherbaine SAR studies could provide new insights into glutamate receptor structure and function.

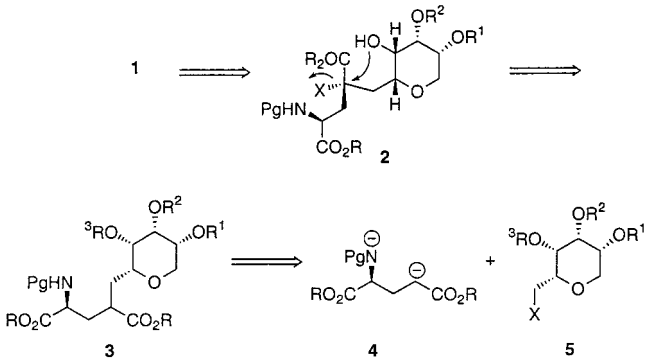
Results and Discussion

Synthetic Planning. The structure of dysiherbaine is that of a hexahydrofuro[3,2-*b*]pyran ring system with a glutamate appendage that presumably occupies the endogenous glutamate active site on the receptor. Dysiherbaine could also be viewed as a γ,γ-disubstituted glutamate; many γ-substituted glutamates are known to show increased receptor selectivity compared to glutamate itself, so from this perspective it is perhaps not surprising that dysiherbaine is an active and selective glutamate receptor ligand.[19−25]

One of the synthetically demanding features of this target is the tetrasubstituted C-4 center. Several groups have developed syntheses of dysiherbaine and simplified analogues, and in all cases procuring the C-4 center stereoselectively posed a significant synthetic challenge.[26−29] A highly stereoselective method, therefore, figured prominently in our synthetic planning, as did increased convergence.

One way to address both of these issues simultaneously would be to dissect the molecule into an appropriately functionalized glutamate (**4**) and a pyran (**5**), which would be joined by a tetrahydrofuran-ring-forming reaction (Scheme 1). In this approach, the stereoselective construction of the tetrahydrofuran ring is the key step, requiring a leaving group at the γ-carbon of glutamate that would be displaced by an oxygen nucleophile on the pyran **2** in an S_N2 fashion. Establishing the correct C-4 stereochemistry would then be predicated upon a stereoselective enolate halogenation of **3** at the γ-position. Intermediate **3** would in turn be obtained via an alkylation of a protected glutamate (**4**) with a glycosyl electrophile (**5**). This overall synthetic strategy is reasonably convergent and, at the same time, could give access to an interesting group of uniquely substituted glutamate analogues for SAR studies.

Scheme 1



Several protecting groups (phenylfluorenyl (PhFl), trityl (Tr), trifluroacetamide, *p*-nitrophenylamide, and carbamates) may be employed for the γ-alkylation of glutamate without epimerization at the α-center. PhFl and Tr completely protect the α-stereocenter from epimerization, but alkylations are often not very stereoselective,[30,31] except in alkylations of PhFl-protected aspartates.[32] Pyroglutamate is an internally protected form of glutamate, and alkylations of protected pyroglutamates have been shown to produce good stereoselectivities.[33,34] More recently, however, Hanessian[35−37] and others[24,25] have shown that amides and carbamates of glutamate diesters undergo efficient and highly diastereoselective alkylations without epimerizing the α-stereocenter. We envisioned a route to dysiherbaine employing two sequential stereoselective enolate reactions of an appropriately protected glutamate, one to form the C−C bond and the other to close the tetrahyrofuran ring via C−O bond formation. Although there were to our knowledge no reports of Hanessian-type reactions of γ-substituted glutamates, there appeared to be no a priori reason that the same model would not apply in such a case.

Total Synthesis. The first stage of this plan required the acquisition of the pyran core. Styractitol (**6**) was prepared from D-(+)-mannose according to known literature procedures[38] and converted into **7** via a TBDPS protection of the primary C-6 alcohol, followed by iso-

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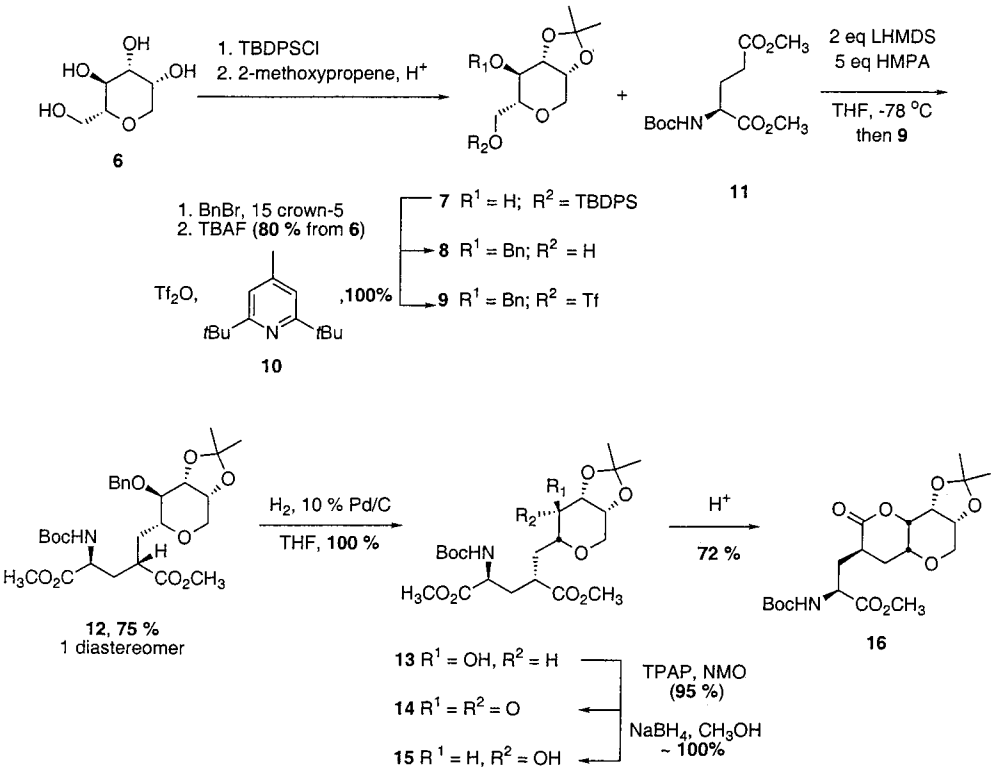
Scheme 2



propylidene ketal formation with 2-methoxypropene (Scheme 2).[39] Benzylation of **7** with sodium hydride and benzyl bromide proved to be quite sluggish. Combinations of elevated temperatures, excess electrophile, excess base, and the use of TBAI produced poor yields; however, upon addition of 15-crown-5 to a THF solution of **7**, benzyl bromide, and NaH at 0 °C, the reaction was nearly complete in 1 h.[40] The crude product was deprotected with TBAF to give the alcohol **8**, which was then converted into the triflate **9**.[41] In the next step, the alkylation that brings together the two major fragments of the target, the LHMDS-generated enolate of **11** was treated with the triflate electrophile **9** to give a single diastereomer (**12**) in excellent yield. The stage was thus set for the crucial γ-functionalization step necessary to carry out the key ring closure.

The ring-closing strategy required the stereoselective installation of a leaving group at the γ-position, as discussed above. Despite the absence of precedents for preparing γ,γ-disubstituted glutamates from the corresponding γ-substituted enolates, this simple strategy appeared to be worth exploring as a means of obtaining the desired γ-halo derivative required for tetrahydrofuran ring closure. However, it quickly became apparent that this strategy was untenable, most likely because the selective deprotonation of **12** failed.

This setback prompted us to consider related systems in which the γ-deprotonation might be more facile. Since lactones are considerably more acidic than their ester counterparts,[42] one such possibility would be to re-engineer this intermediate so that the distal carboxyl group is in the form of a δ-lactone. This modification in turn suggested the possibility of employing an interesting variant of the original strategy for tetrahydrofuran ring formation that would rely on the ring contraction of α-halo-, α-mesyl-, and α-triflyl-δ-lactones developed by Fleet.[43−53] Specifically, when such lactones are treated with a nucleophile, attack at the carbonyl group predominates, leading to ring opening followed by attack of the newly unveiled alkoxide on the α-center that bears the leaving group. Since the S_N2 reaction proceeds with clean inversion, this method would offer a simple and convenient means of controlling the stereochemistry of the C-4 position in dysiherbaine, assuming that the α-leaving group could be introduced diastereoselectively.

To implement this revised plan, the C-7 alcohol group on the pyran ring would be internally acylated to form the lactone, but before that it would have to be inverted. Both steps were readily accomplished by treatment of **12**

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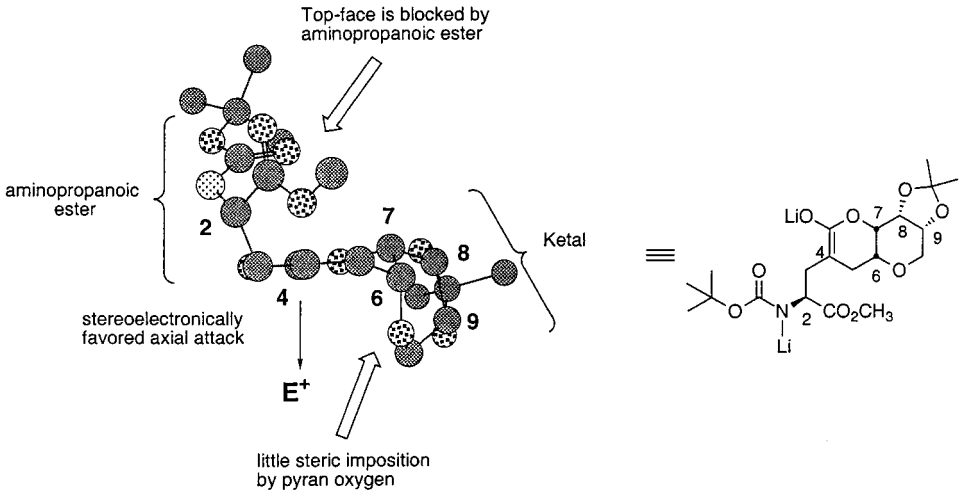

Figure 2. Conformation of the enolate of lactone **21**.

with Pd/C and H_2 in THF to give **13** (Scheme 2), which was followed by TPAP/NMO oxidation[54] to give **14**, and reduction of the ketone with $NaBH_4$ in methanol at −20 °C to give **15**. Treatment with a catalytic amount of acid then gave the requisite lactone **16**.[6,7]

Obtaining the natural C-4 stereochemistry in this sequence is clearly contingent on selective enolate halogenation in the correct stereochemical sense, but it initially appeared that this reaction would likely occur on the "wrong" face of the lactone enolate **21**; one might expect attack from the seemingly less hindered convex side (Figure 2), which would ultimately produce the epimer of the desired tetrahydrofuran product. Although this stereochemical conundrum might seem to doom this route, there is precedent suggesting that more subtle factors might intervene in this system to give the desired result. Tomioka et al. have shown that the dominant factor in determining the stereochemical outcome of similar δ-lactone alkylations is the size of the α-substituent.[55] In the specific case of the enolate derived from **16**, according to the Tomioka model, there would be several low-energy conformations in which the aminopropanoic ester moiety essentially blocks the top face of the enolate.[56] The validity of this model aside, the pseudoaxial pyran oxygen is not sterically demanding, and the ketal group does not appear to play a key role in biasing attack on the enolate; hence, stereoselective halogenation might result from stereoelectronically favored axial attack to give the desired diastereomer.

In a further interesting complication, because of the presence of the internal carbamate anion in this particular lactone enolate, the initially formed α-halolactone could proceed directly to the desired bicyclic ring system without isolation of the α-halide itself. Specifically, halogenation of the lactone enolate in the presence of the internal carbamate anion could trigger the intramolecular opening of this lactone (**22**) to give **23**, which would then undergo halide displacement by the newly unveiled alkoxide, leading to the tetrahydrofuran **24** (Scheme 3, pathway 1). This possibility also raises the issue of whether the carbamate anion might attack the lactone carbonyl *before* the lactone enolate is formed, leading to the pyroglutamate **19** (Scheme 3, pathway 2). Enolization of **19** would then give the corresponding enolate **20**, a species for which there is ample precedent for excellent diastereoselectivity in reactions with electrophiles.[34] In this case, halogenation would be expected to occur on the opposite face relative to the C-2 ester group to give **23**, the penultimate intermediate in pathway 1. Ring closure of **23**, regardless of which pathway is followed, would then give **24** with good control of C-4 stereochemistry.

All of these factors provided substantial encouragement to forge ahead with the Fleet ring-contraction plan. It was therefore gratifying to find that our stereochemical prediction for the halogenation was correct (on the basis of the conversion of this intermediate into dysiherbaine; see below), and that the initial reaction did proceed in situ to form the desired bicyclic acid **25**. When the lactone **16** was treated with 2 equiv of base followed by any of a variety of halogen sources (i.e., I_2,[57,58] CBr_4,[59,60] NBS), the tetrahydrofuroic acid **25** was isolated directly, along with unreacted starting material and compound **26** in varying amounts (Scheme 4). When the reaction was quenched under anhydrous acidic conditions (HOAc/THF), the tetracyclic imide **24** could be isolated, but it decomposed when silica gel chromatography was attempted. This material could, however, be converted into the more stable methyl ester with methanol/methoxide.[61−63] The best conditions for this one-pot, multistep cascade are NaHMDS, I_2, and an alkaline bisulfite workup, which gives **25** in 48% yield and **26** in 14% yield.

We were then poised to complete the synthesis of dysiherbaine by converting the equatorial C-8 oxygen into

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(56) The conformation shown in Figure 2 was minimized using the MM2 force field with the Chem3D software package (CambridgeSoft). The conformation shown is simply our interpretation of the Tomioka model discussed in the text. There are clearly other conformations in which the steric differentiation of the two faces of the enolate is less pronounced.

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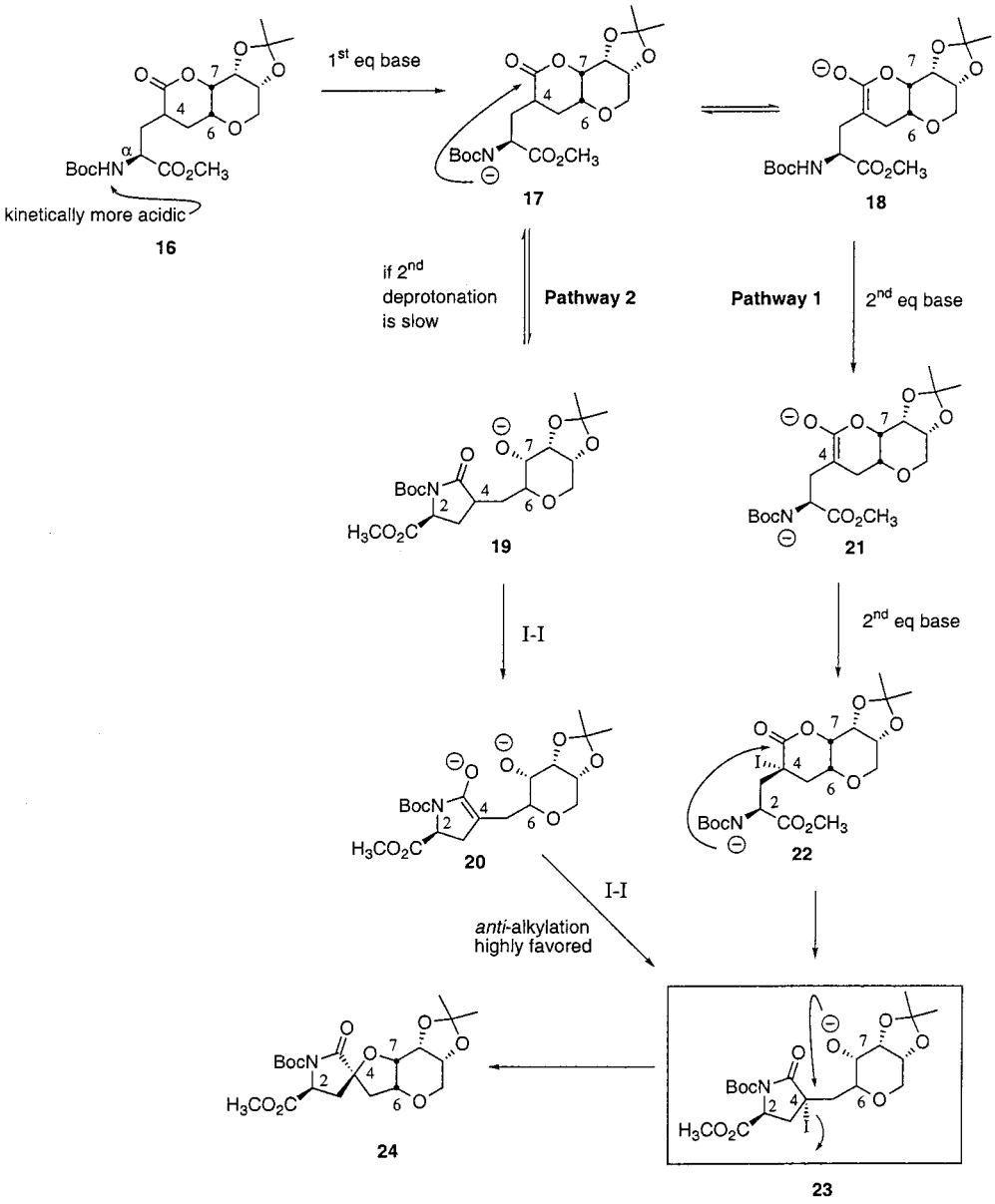
Scheme 3



the required methylamino group. The acid **25** was converted into **27** with (TMS)CHN_2, followed by ketal deprotection with ferric chloride adsorbed on silica gel to give the diol **28** in near quantitative yield. NMR analysis of **28** (NOE and COSY) confirmed that the correct C-4 stereochemistry had been obtained, as did subsequent conversion into dysiherbaine. Although it has not been determined which of the alternative pathways is being followed, halogenation clearly does occur from the face predicted by either model to give the stereochemistry leading to dysiherbaine.

At this point, with the diol unveiled, chemoselective oxidation of the equatorial alcohol **28** was required for introducing the methylamino group by reductive amination. A number of oxidation conditions were tested, including conversion into the stannyl acetal followed by bromine oxidation,[64] Swern oxidation,[65] PCC oxidation,[66] and Dess−Martin periodinane,[67,68] but TPAP/NMO[54] gave consistently higher yields of the intermediate ketol than any other conditions surveyed. The resultant hydroxy ketone intermediate proved to be unstable to both silica gel and alumina chromatography, which made a one-pot oxidation/reductive amination sequence necessary.

The one-pot oxidation/reductive amination was carried out by performing the TPAP/NMO oxidation following standard conditions; when the reaction was complete, ethanol was added to quench the oxidant and act as a cosolvent for the reductive amination reaction.[69] Isolation of the very polar amino alcohol proved to be difficult, so upon completion of the one-pot oxidation/reductive amination and workup, the crude amino alcohol was Boc-protected to give **29** in 18% yield (three steps + 8% recovered **28**), a three-step yield that suffers most likely from the instability of the hydroxy ketone intermediate.

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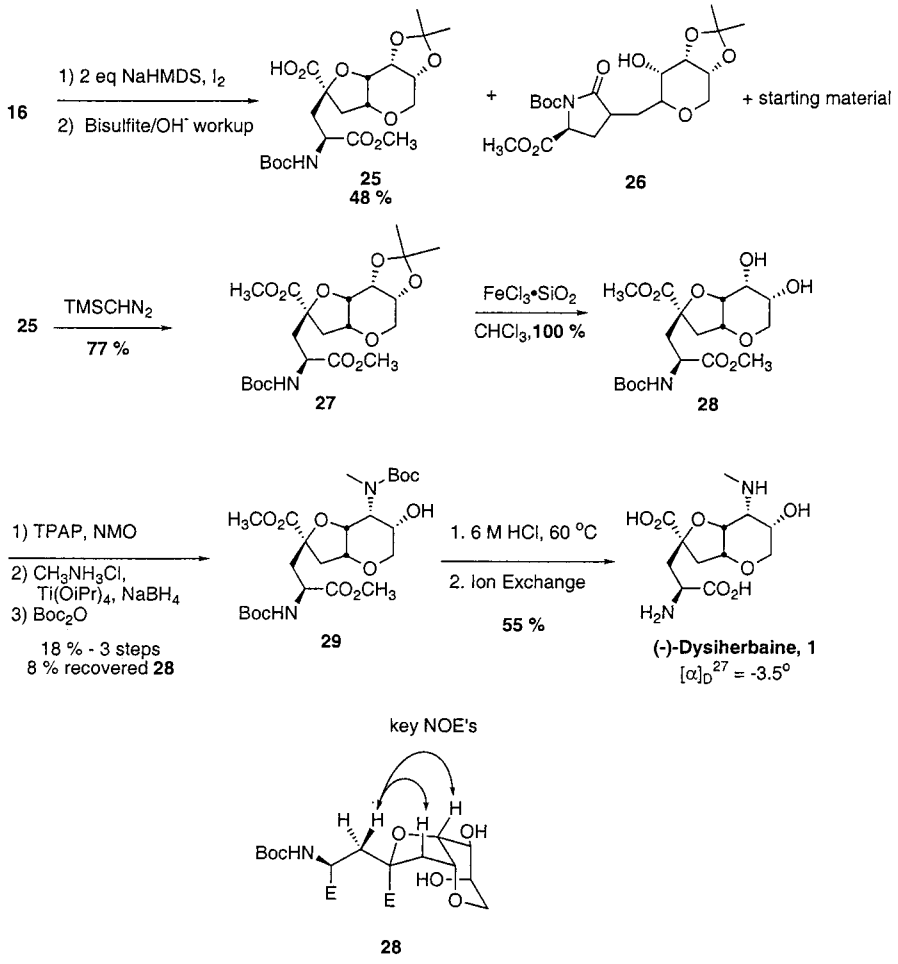
Scheme 4



Finally, hydrolysis of **29** with 6 M HCl and ion exchange chromatography gave **1**, which proved identical in all respects to the natural material (^{1}H NMR, ^{13}C NMR, HRMS, and optical rotation).

Conclusion

A convergent synthesis of the glutamate receptor agonist dysiherbaine was achieved by applying a novel and stereoselective one-pot halogenation−ring-contraction reaction to prepare the bicyclic ring system with excellent stereochemical control of the C-4 center. This extension of the Fleet ring-contraction reaction allowed us to prepare the natural product in fewer steps and with greater control of stereochemistry than in previously reported syntheses. The route is also amenable to analogue preparation SAR analysis, which is currently under way.

Experimental Section

General Procedures. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), and diethyl ether were filtered through two columns of activated basic alumina and transferred under Ar(g) in a solvent purification system designed and manufactured in house by J. C. Meyer. Dry toluene was obtained similarly on the system by filtering through two columns of Q5. Dry dimethylformamide (DMF) was obtained by passing through two columns of activated molecular sieves. Triethylamine (TEA), hexamethylphosphoramide (HMPA), hexamethyldisilazane (HMDS), and methanol (MeOH) were purified by distillation from calcium hydride. Unless otherwise noted, all crude reaction mixtures were dried over solid magnesium sulfate ($MgSO_4$), filtered, and concentrated in vacuo on a rotary evaporator. Abbreviations: ethyl acetate (EtOAc), camphorsulfonic acid (CSA), *N*-methylmorpholine *N*-oxide (NMO), tetrapropylammonium perruthenate (TPAP), magnesium sulfate ($MgSO_4$) 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). All other reagents were used as purchased from Aldrich, Sigma-Aldrich, or Acros unless otherwise stated.

Protection of 6 (7). Compound **6** (7.50 g, 45.7 mmol) was dissolved in dry DMF (230 mL) and cooled in an ice bath. Imidazole (3.42 g, 50.2 mmol) and (TBDPS)Cl (13.2 mL, 47.9 mmol) were added, and the solution was stirred at 0 °C for 3 h, followed by the addition of 2-methoxypropene (5.47 mL, 57.1 mmol) and CSA (2.12 g, 9.1 mmol). After an additional 2 h the reaction was treated with a solution of 5% bicarbonate (100 mL) and then extracted with diethyl ether (3 × 125 mL). The combined organic layers were washed with water (5 × 100 mL), concentrated, and purified by flash chromatography (50% ether/hexanes) to yield the title compound (16.9 g, 84%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.42 (m, 6H), 4.24 (d, J = 13.6 Hz, 1H), 4.18 (dd, J = 5.7, 2.2 Hz, 1H), 4.03 (dd, J = 7.0, 5.7 Hz, 1H), 3.93 (dd, J = 10.7, 4.6 Hz, 1H), 3.88−3.83 (m, 2H), 3.69 (dd, J = 13.5, 2.4 Hz, 1H), 3.14 (app quintet, J = 4.9 Hz, 1H), 2.92 (br s, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.5, 132.8, 132.6, 129.9, 129.8, 127.8, 127.7, 109.6, 79.1, 77.1, 73.6, 72.4, 66.4, 65.1, 28.2, 26.8, 26.3, 19.2; IR (thin film) 3448, 3070, 2932, 2856, cm^{-1}; HRMS (CI) calcd for $C_{24}H_{31}O_5$ [M − CH_3]$^+$ 427.1940, found 427.1923; $[\alpha]_D^{25}$ −41.282° (*c* 5, MeOH).

Alcohol 8. Compound **7** (15.85 g, 35.8 mmol) was dissolved in dry THF (140 mL) and cooled to 0 °C. Sodium hydride (1.576 g (60 wt %), 39.4 mmol) was then added portionwise over 2 min. After the mixture was stirred for 10 min, benzyl bromide (5.0 mL, 39.4 mmol) was added slowly, followed 5 min later by dropwise addition of 15-crown-5 (7.11 mL, 35.8 mmol). The

reaction mixture was stirred at 0 °C for 30 min and then room temperature for 2 h. It was then poured onto ice (~200 g) and extracted with EtOAc (2 × 100 mL). The organic layer was washed with brine (100 mL) and then concentrated to give the crude product as an oil, which was dissolved in THF (140 mL) and treated with a 1 M TBAF solution (40 mL, 40 mmol). After 2 h the reaction was concentrated and purified by flash chromatography (50% EtOAc/hexanes) to give the title compound (6.88 g, 65%) as a clear, colorless oil. Upon prolonged standing the material became a white semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.88 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.29−4.27 (m, 3H), 3.87 (dd, J = 11.5, 2.38 Hz, 1H), 3.74 (dd, J = 13.5, 2.1 Hz, 1H), 3.66 (dd, J = 11.6, 6.0 Hz, 1H), 3.51 (dd, J = 9.7, 6.3 Hz, 1H), 3.20 (ddd, J = 9.5, 5.8, 3.5 Hz, 1H), 2.04 (br s, 1H), 1.53 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 128.3, 128.0, 127.7, 109.4, 79.2, 77.9, 76.7, 73.9, 72.7, 66.6, 62.9, 27.9, 26.2; HRMS (CI) calcd for $C_{16}H_{22}O_5$ [M$^+$] 294.1467, found 294.1473; IR (thin film) 3448, 3072, 3025, 2989, 1450 cm^{-1}; $[\alpha]_D^{25}$ −9.5° (*c* 0.7, CH_2Cl_2).

Triflate 9. Alcohol **8** (3.12 g, 10.6 mmol) was placed in an oven-dried flask, concentrated from toluene (2 × 25 mL) under high vacuum, and then dissolved in DCM (75 mL), treated with DTBMP (2.65 g, 12.9 mmol), and cooled to −55 °C. Trifluoromethanesulfonic anhydride (2.14 mL, 12.7 mmol) was added dropwise, and after being stirred at −55 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 30 min. Diethyl ether (80 mL, purified) was added, and the mixture was filtered on a Hirsch funnel to remove white pyridinium triflate. The filter cake was rinsed with ether, and the filtrate was then filtered once again, washed successively with 5% aqueous bicarbonate (1 × 25 mL) and brine (1 × 25 mL), and then concentrated to give a slightly colored oil. Flash chromatography (30% ether/70% light petroleum ether) gave 4.252 g (94%) of the title compound as a white solid, which was used immediately in the subsequent reaction without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.20 (m, 5H), 4.90 (d, J = 11.5 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.51 (dd, J = 10.7, 6.2 Hz, 1H), 4.29 (d, J = 13.7 Hz, 1H), 4.25 (d, J = 5.7 Hz, 1H), 4.24 (dd, J = 5.8, 2.0 Hz, 1H), 3.74 (dd, J = 13.6, 2.2 Hz, 1H), 3.49−3.39 (m, 2H), 1.54 (s, 3H), 1.40 (s, 3H); IR (thin film) 3000, 2998, 1451, cm^{-1}.

Glutamate Adduct 12. Compound **11** (4.14 g, 15.0 mmol) was concentrated from dry toluene (2 × 25 mL) and placed under high vacuum overnight prior to use. The resultant oil was dissolved in dry THF (75 mL) and cooled to −78 °C. In a separate flask 0.64 M LHMDS (32.0 mmol), freshly prepared from a 1.8 M solution of *n*-BuLi (17.9 mL 32.3 mmol) and HMDS (7.50 mL, 35.5 mmol) in 25 mL of THF, was cooled to −78 °C, and then it was cannulated dropwise into the flask containing **11** over a 20 min period. After 1 h, HMPA (13.0 mL, 75 mmol) was added dropwise to the solution, and the solution was stirred for an additional 20 min. A separate flask containing the triflate **9** (3.50 g, 8.21 mmol) was charged with THF (20 mL), which was cooled to −78 °C and then added dropwise via cannula over 20 min to the solution of the dianion. After 7 h, the reaction was warmed to −30 °C, stirred for approximately 5 min, and then quenched by adding 1 M HCl (40 mL), stirring vigorously for 15 min, and warming to 0 °C. The reaction was then extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with saturated ammonium chloride until the pH of the aqueous layer was acidic. Successive washes with brine (2 × 25 mL) and concentration gave the crude product. Flash chromatography (25% EtOAc/hexanes ramped to 50% EtOAc/hexanes) gave the title compound (3.41 g, 75%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 4.96 (d, J = 8.0 Hz, 1H), 4.87 (d, J = 11.5 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.31 (m, 1H), 4.17 (m, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 3.60 (m, 1H ovrlp with OCH_3), 3.23 (dd, J = 9.5, 5.9 Hz, 1H), 3.07 (d, J = 8.8, 1H), 2.64 (m, 1H), 2.10−1.97 (m, 3H), 1.71 (ddd, J = 14.3, 9.8, 6.8 Hz, 1H), 1.51 (s, 3H), 1.42 (s, 9H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 172.8, 154.8, 138.0, 128.3, 128.0, 127.7, 109.4, 79.8 (×2), 79.4, 75.9, 74.0, 72.7, 66.5, 52.5, 52.3, 51.7, 39.3, 34.9, 33.8, 28.3, 28.0, 26.3; IR (thin film) 3354, 3033, 2979, 2923, 1735, 1710, 1506 cm^{-1}; HRMS (CI) calcd for $C_{28}H_{41}NO_{10}$ [M + H]$^+$ 552.2802, found 552.2810; $[\alpha]_D^{25}$ −7.3° (*c* 1.4, CH_2Cl_2).

Alcohol 13. Compound **12** (3.43 g, 6.21 mmol) was dissolved in THF (100 mL) and charged with 10% Pd/C (660 mg, 0.62 mmol, 10 mol %). The reaction vessel was fitted with a balloon containing H_2 (approximately 1 atm). After 1 h the reaction mixture was filtered on a pad of Celite, rinsed with EtOAc, and concentrated to dryness to give the title compound (2.85 g, 99%) as a white foam that was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (d, J = 8.6 Hz, 1H), 4.36 (m, 1H), 4.20 (d, J = 13.7 Hz, 1H), 4.16 (dd, J = 5.8, 2.4 Hz, 1H), 3.94 (dd, J = 6.4, 6.4 Hz, 1H), 3.72 (s, 3H), 3.68−3.64 (m, 1H ovrlp with OCH_3), 3.66 (s, 3H), 3.43−3.37 (m, 1H), 3.02 (ddd, J = 9.0, 9.0, 2.5 Hz, 1H), 2.70 (app quintet, J = 6.7 Hz, 1H), 2.44, (br s, 1H), 2.07−1.99 (m, 3H), 1.86 (ddd, J = 15.3, 15.3, 7.9, 1H), 1.52 (s, 3H), 1.43 (s, 9H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 172.7, 155.3, 109.5, 79.9, 79.4, 76.6, 73.9, 73.6, 66.4, 52.3, 52.1, 51.8, 39.1, 34.2, 34.0, 28.2, 28.1, 26.2; IR (thin film) 3445, 3356, 2981, 1716, cm^{-1}; HRMS (CI) calcd for $C_{21}H_{35}NO_{10}$ [M + H]$^+$ 462.2339, found 462.2327; $[\alpha]_D^{25}$ −37.3° (*c* 2.1, CH_2Cl_2).

Ketone 14. Alcohol **13** (2.32 g, 5.0 mmol) was dissolved in DCM (35 mL) and added via cannula to a flame-dried flask containing freshly activated 4 Å molecular sieves (~2.8 g). NMO (755 mg, 6.25 mmol) was added followed by TPAP (68 mg, 0.25 mmol, 5 mol %) and the reaction mixture stirred for 1 h. The reaction mixture was filtered on a pad of silica gel, rinsed with EtOAc, concentrated, and purified by flash chromatography (70% EtOAc/hexanes) to give the title compound (2.00 g, 87%) as a pure white powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, J = 9.0 Hz, 1H), 4.60 (d, J = 6.2 Hz, 1H), 4.41 (d, J = 6.2 Hz, 1H), 4.34 (m, 1H), 4.17 (d, J = 12.4 Hz, 1H), 3.85 (m, 2H signals ovrlp), 3.73 (s, 3H), 3.66 (s, 3H), 2.66 (app quintet, J = 6.5 Hz, 1H), 2.12−1.99 (m, 4H), 1.46 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 175.5, 172.7, 155.4, 111.2, 80.1, 79.9, 77.5, 77.4, 66.9, 52.5, 52.3, 52.0, 39.0, 34.2, 31.6, 28.4, 27.1, 25.9; IR (thin film) 3356, 2980, 1738 cm^{-1}; HMS (CI) calcd for $C_{21}H_{33}NO_{10}$ [M + H]$^+$ 460.2182, found 460.2181; $[\alpha]_D^{25}$ +10.9° (4.5, CH_2Cl_2).

Alcohol 15. Ketone **14** (2.48 g, 5.4 mmol) was dissolved in dry MeOH (30 mL) and cooled to −20 °C. Solid sodium borohydride (500 mg, 13.5 mmol) was added in one portion, and the reaction mixture was stirred for 10 min and then poured into a rapidly stirred solution of DCM (50 mL) and 0.15 M pH 7 phosphate buffer (50 mL). After 10 min, the layers were separated, the aqueous layer was extracted with DCM (2 × 30 mL), and the combined organic layers were concentrated. Flash chromatography (60% EtOAc/hexanes) gave the title compound (2.48 g, 100%) as a pure white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (d, J = 8.3 Hz, 1H), 4.34 (m, 1H), 4.25 (d, J = 13.5 Hz, 1H), 4.11 (m, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 3.58 (app d, J = 7.4 Hz, 1H), 3.61 (dd, J = 9.3, 3.8 Hz, 1H), 2.62 (app quintet, J = 6.9 Hz, 1H), 2.27 (d, J = 7.6 Hz, 1H), 2.20 (ddd, J = 14.2, 8.8, 8.8 Hz, 1H), 2.04 (m, 2H), 1.71 (ddd, J = 12.0, 7.1, 7.1 Hz, 1H), 1.56 (s, 3H), 1.43 (s, 9H, 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 172.6, 155.3, 109.2, 79.9, 75.2, 73.2, 71.0, 66.8, 66.5, 52.3, 52.1, 51.8, 39.4, 34.3, 34.2, 28.2, 25.7, 25.3; IR (thin film) 3550, 3351, 2972, 1730, cm^{-1}; HRMS (CI) calcd for $C_{21}H_{35}NO_{10}$ [M + H]$^+$ 462.2339, found 462.2334; $[\alpha]_D^{25}$ −26.1° (2.7, CH_2Cl_2).

Lactone 16. Alcohol **15** (2.45 g, 5.3 mmol) was dissolved in benzene (260 mL) and treated with CSA (163 mg, 0.70 mmol, 13 mol %) and pyridine (0.05 mL, 0.5 mmol). The flask was then equipped with a Soxhlet extractor containing activated 5 Å molecular sieves and the reaction mixture heated at reflux for ~72 h, cooled to room temperature, treated with 5 mL of TEA, and concentrated. The crude product was dissolved in EtOAc (50 mL) and washed successively with 5% aqueous bicarbonate (1 × 15 mL) and brine (1 × 15 mL). The combined organic layers were then concentrated. Flash chromatography (50% EtOAc/hexanes → 70% EtOAc/hexanes) gave the title compound (1.65 g, 72%) as a white foam. The product was an inseparable mixture of diastereomers and was used without

further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (d, J = 8.8 Hz, 1H), 4.42 (dd, J = 5.2, 3.0 Hz, 1H), 4.37−4.31 (m, 2H), 4.22 (d, J = 13.7 Hz, 1H), 4.15 (dd, J = 5.9, 2.6 Hz, 1H), 3.73 (s, 3H), 3.71−3.66 (m, overlp diastereomer, 2H), 3.01 (m, 1H), 2.44 (m, 1H), 2.29 (ddd, J = 14.6, 10.3, 4.7 Hz, 1H), 2.01−1.95 (m, 1H), 1.84−1.70 (m, overlp diastereomer, 1H), 1.63 (s, 3H), 1.42 (s, 9H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 172.1, 155.2, 110.4, 80.1, 73.7, 71.8, 70.8, 68.8, 67.0, 52.5, 50.9, 34.3, 30.9, 28.4, 26.0, 25.8; IR (thin film) 3354, 2981, 1786, 1715 cm^{-1}; HRMS (CI) calcd. for $C_{19}H_{28}NO_9$ [M − Me]$^+$ calcd 414.1764, found 414.1758.

Acid 25. Lactone **16** (750 mg, 1.74 mmol) was dissolved in THF (6.5 mL) and cooled to −78 °C. A separate flask was charged with NaHMDS (1 M in THF, 4.0 mL, 4.0 mmol) in THF (7.5 mL) and cooled to −78 °C. The solution containing **16** was added dropwise to the NaHMDS solution over 10 min, resulting in a bright yellow solution that was stirred for an additional 30 min. A third flask containing I_2 (467 mg, 1.84 mmol) in THF (9.0 mL) was cooled to −78 °C, and the yellow dianion was then added to the I_2 solution via cannula over a 10 min period. The reaction mixture was stirred for 1 h at −78 °C and then 30 min at −20 °C. It was quenched with 0.1 N LiOH (0.5 mL) in THF (5 mL), stirred for 20 min, and then allowed to warm to room temperature. A dilute alkaline bisulfite solution (water (8 mL), 5% bisulfite (1 mL), and 1 N LiOH (1 mL)) was added and the resultant solution stirred rapidly for an additional 10 min. The reaction mixture was concentrated in vacuo to approximately one-third of the initial volume and extracted with EtOAc (30 mL). The organic layer was washed with a 1% aqueous bicarbonate (2 × 15 mL), and the combined aqueous layers were acidified to pH 3 with 0.1 N HCl. Solid sodium chloride (∼5 g) was then added to the aqueous solution, which was then extracted with EtOAc (3 × 20 mL). The combined organic layers were concentrated and purified by flash chromatography (60% EtOAc/hexanes → 80% EtOAc/hexanes → 90% EtOAc/10% ^{i}PrOH) to give the title compound (376 mg, 48%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (br s, 1H), 5.33 (d, J = 6.5 Hz, 1H), 4.39−4.35 (m, two ovrlp signals, 2H), 4.24 (d, J = 14.0 Hz, 1H), 4.16 (app d, J = 4.4 Hz), 4.13 (dd, J = 2.5, 2.5 Hz, 1 H), 4.02 (ddd, J = 4.4, 4.4, 2.3, 1H), 3.74 (s, 3H), 3.63 (dd, 13.9, 2.2 Hz, 1H), 2.76 (dd, J = 14.5, 5.9 Hz, 1H), 2.57 (d, J = 13.9 Hz, 1H), 2.22 (dd, J = 13.6, 4.0 Hz, 1H), 2.10 (dd, J = 14.4, 3.10 Hz, 1H), 1.64 (s, 3H), 1.43 (s, 9H), 1.18 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 172.3, 155.0, 110.5, 83.6, 80.0, 77.2, 75.1, 70.7, 64.9, 52.4, 50.8, 45.7, 39.1, 36.4, 28.3, 25.8, 25.4; IR (thin film) 3400 (br), 2924, 1750, 1708 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{31}NO_{10}$ [M + Na]$^+$ 468.1845, found 468.1845.

Methyl Ester 27. Acid **25** (240 mg, 0.53 mmol) was dissolved in DCM (6 mL) and MeOH (1 mL) and treated with $(TMS)CHN_2$ (2.0 M in hexanes, 0.5 mL, 1 mmol) for 5 min. Acetic acid (0.5 mL) was added, followed by EtOAc (10 mL). Successive washes with 5% bicarbonate (10 mL) and brine (10 mL) were followed by concentration of the combined organic layers to give the crude ester. Purification by flash chromatography (50% EtOAc/hexanes) gave the title compound (190 mg, 77%) as a pure white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (d, J = 6.5 Hz, 1H), 4.39 (dd, J = 6.6, 4.9 Hz 1H), 4.27 (dd, J = 11.2, 5.6 Hz, 1H), 4.10 (m, 2H), 3.99 (m, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.71 (d, J = 2.2 Hz, 1H), 3.50 (dd, J = 13.3, 2.7 Hz, 1H), 2.63 (dd, J = 13.7, 3.9 Hz, 1H), 2.48 (dd, J = 14.5, 5.0 Hz, 1H), 2.23 (dd, J = 13.6, 6.1 Hz, 1H), 2.18 (dd, J = 14.6, 5.8 Hz, 1H), 1.61 (s, 3H), 1.43 (s, 9H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 172.1, 155.1, 110.5, 83.4, 79.8, 75.6, 75.3, 71.5, 71.2, 66.5, 52.5, 52.3, 51.2, 44.2, 39.9, 28.3, 25.9, 25.8; IR (thin film) 3385, 2979, 1715 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{33}NO_{10}$ [M + H]$^+$ 460.2182, found 460.2190; $[\alpha]_D^{27}$ +17.1° (*c* 0.8, $CHCl_3$).

Diol 27. Methyl ester **27** (165 mg, 0.36 mmol) was dissolved in $CHCl_3$ (7 mL) and treated with $FeCl_3$·SiO_2 (100 mg) and acetic acid (0.1 mL). After being stirred for 17 h, the reaction mixture was filtered through a pad of SiO_2, washed with EtOAc, and concentrated. Flash chromatography provided the title compound (156 mg, 99%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (d, J = 6.2 Hz, 1H), 4.34 (dd, J = 9.5, 6.0 Hz, 1H), 4.03 (m, 1H), 3.99−3.96 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.68 (br s, 1H), 3.64 (dd, J = 3.8, 3.8 Hz, 1H), 3.42 (d, J = 11.9 Hz, 1H), 2.81 (dd, J = 14.5, 5.4 Hz, 1H), 2.53 (d, J = 14.0 Hz, 1H), 2.26 (dd, J = 14.6, 3.7 Hz, 1H), 2.13 (dd, J = 14.1, 3.6 Hz, 1H), 1.60 (br s, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 172.2, 155.0, 83.2, 81.0, 80.0, 76.6, 70.1, 67.7, 67.2, 53.0, 51.0, 4.61, 40.3, 28.3; IR (thin film) 3425, 1741, 1709 cm^{-1}; HRMS (CI) calcd for $C_{18}H_{29}NO_{10}$ [M + NH_4]$^+$ 437.2135, found 437.2144; $[\alpha]_D^{27}$ +56.7° (*c* 1.1, $CHCl_3$).

Protected Dysiherbaine 29. A flask containing diol **27** (75 mg, 0.2 mmol) and activated molecular sieves (4 Å beads) was charged with DCM (3 mL), and the solution was cooled to 0 °C. NMO (63 mg, 0.54 mmol) and TPAP (10 mg, 0.03 mmol) were added, and the solution was stirred for 10 min. Dry ethanol (3 mL) was then added, and the reaction mixture was stirred for an additional 15 min. Methylamine hydrochloride (60 mg, 0.9 mmol), TEA (0.13 mL, 0.9 mmol), and $Ti(OiPr)_4$ (0.25 mL, 0.9 mmol) were added in succession, and after the solution was stirred for 1.5 h, sodium borohydride (20 mg, 0.5 mmol) was added. After an additional 1.5 h the reaction was quenched with 2.5% NH_4OH (1 mL) and stirred for 5 min. The insoluble inorganic precipitate was filtered on a thin pad of Celite and rinsed with EtOAc. The organic layers were combined and concentrated to give a light brown solid that was taken up in EtOAc (5 mL) and filtered through another narrow pad of Celite. The pad was washed with EtOAc/MeOH (90:10) and again concentrated to dryness. Addition of DCM produced a white precipitate that was filtered off, and the filtrate was refiltered through a cotton plug and rinsed with DCM. The concentrated organic layers were dissolved in MeOH (2 mL), treated with NEt_3 (0.1 mL) and Boc_2O (0.2 mL), and then stirred overnight. The reaction mixture was diluted with EtOAc (10 mL) and washed successively with 2.5% $NaHSO_4$ (2 × 4 mL) and brine (1 × 3 mL). The combined organic layers were concentrated, and the resultant product was purified twice by flash chromatography (2.5% MeOH/DCM) to give the title compound (16 mg, 17%) as a white solid along with recovered **27** (6 mg, 8%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (br s, 1H), 4.92 (d, J = 12.6 Hz, 1H), 4.46 (br s, 1H), 4.24 (m, 1H), 4.13 (dd, J = 1.3, 1.3 Hz, 1H), 4.03 (d, J = 1 Hz, 1H), 3.84 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.80 (ovrlp m, 1H), 3.72 (s, 3H), 3.55 (d, J = 12.1 Hz, 1H), 3.27 (s, 3H), 2.63 (dd, J = 14.5, 4.7 Hz, 1H), 2.53 (d, J = 14.0 Hz, 1H), 2.09 (dd, J = 14.4, 7.5 Hz, 1H), 2.03 (m, 1H), 1.47 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 172.1, 155.6, 155.2, 85.3, 82.4, 79.9, 77.7, 73.1, 69.0 53.1, 52.6, 52.3, 51.3, 44.7, 39.8, 33.4, 27.7, 28.4, 28.2; IR (thin film) 3443, 2977, 1744, 1716, 1684 cm^{-1}; HRMS (CI) calcd for $C_{24}H_{40}N_2O_{11}$ [M + H] 533.2710, found 533.2697; $[\alpha]_D^{27}$ +58.0° (*c* 0.6, $CHCl_3$).

Dysiherbaine (Synthetic) (1). Compound **29** (11.5 mg. 0.02 mmol) was heated in 6 M HCl (1 mL) at 80 °C overnight and concentrated to dryness in vacuo and then twice more from water to give a quantitative yield of the bis-HCl salt, which was then filtered through AG-1-X2 (acetate form) resin, eluting the neutral product with water. Ninhydrin positive fractions were lyophilized to give **1** (3.6 mg, 55%) as a pure, white amorphous solid: ^{1}H NMR (500 MHz, D_2O) δ 4.47 (dd, J = 1.8, 1.8 Hz, 1H), 4.33 (s br, 1H), 4.03 (dd, J = 12.8, 2.3 Hz, 1H), 4.01 (s br, 1H), 3.71−3.69 (m, 2H), 3.67 (dd, J = 11.7, 2.5 Hz, 1H), 2.95 (s, 3H), 2.75 (dd, J = 15.2, 2.5 Hz, 1H), 2.74 (d, J = 14.0 Hz, 1H), 2.32 (dd, J = 14.0, 3.4 Hz, 1H), 2.09 (dd, J = 15.2, 11.7 Hz, 1H); ^{13}C NMR (125 MHz, D_2O, referenced to the chemical shift of C-6 (77.0 ppm) δ 181.0, 174.6, 89.4, 77.0, 75.7, 69.5, 63.0, 57.3, 54.5, 45.2, 40.1, 30.4; HR ESI-MS [M + Na]$^+$ calcd 327.1168, found 327.1162; $[\alpha]_D^{27}$ −3.6° (*c* 0.1, H_2O).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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