

Total Synthesis of (–)-Dysiherbaine

Hidekazu Masaki, Junji Maeyama, Kazuko Kamada, Tomoyuki Esumi, Yoshiharu Iwabuchi, and Susumi Hatakeyama*

Faculty of Pharmaceutical Sciences
Nagasaki University, Nagasaki 852-8521, Japan

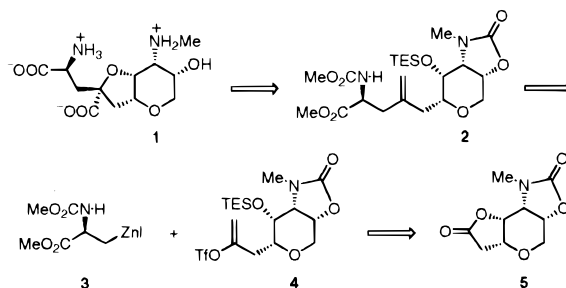
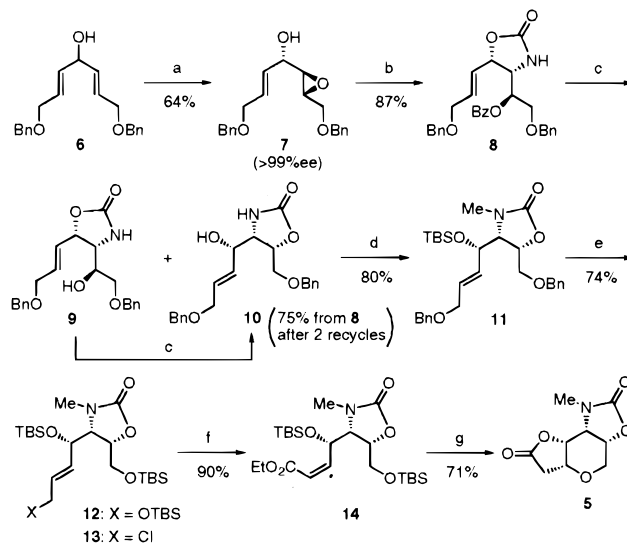
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(–)-Dysiherbaine (**1**), a potent neuroexcitotoxin, was isolated by Sakai and co-workers from a Micronesian sponge *Dysidea herbacea* and found to be a selective agonist of non-NMDA (N-methyl-D-aspartate) type glutamate receptors in the central nervous system.¹ Structurally, this amino acid is characterized by a novel *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamic acid appendage. The relative configuration was determined by detailed NMR analysis;¹ however, the absolute configuration was not elucidated. Its low availability from natural sources, combined with the entirely novel molecular architecture and the potent neuroexcitatory activity, makes **1** an attractive target for synthetic studies.² Its potential as a lead for developing selective agonists or antagonists of glutamate receptors makes the availability of analogues also an important goal.³ We now report an enantioselective total synthesis⁴ of (–)-dysiherbaine (**1**) in naturally occurring form.

We envisaged tetra-substituted pyran **2** as a precursor of **1** and postulated that this intermediate could be accessed via palladium-catalyzed cross-coupling reaction of organozinc reagent **3** and vinyl triflate **4**, accessible from tricyclic lactone **5**, based on Jackson's protocol⁵ (Scheme 1). This coupling process is particularly challenging since Jackson's methodology has not been successfully applied to highly functionalized vinyl triflates such as **4**.⁶ In this synthetic plan, another key issue which must be addressed is the efficient enantioselective construction of tricyclic lactone **5** having four contiguous *cis* stereogenic centers.

Preparation of key compound **5** began with conversion of σ -symmetrical divinylcarbinol **6** to epoxy alcohol **7** using methodology we have previously developed⁷ (Scheme 2). Thus, Katsuki–Sharpless catalytic asymmetric epoxidation^{8,9} of **6**,

Scheme 1

Scheme 2^a

^a Reagents: (a) (i) D-DIPT (9 mol %), Ti(O-*i*-Pr)₄ (7 mol %), *t*-BuOOH (2 equiv), 4A molecular sieves, CH₂Cl₂, –25 °C; (ii) DIPAD, Ph₃P, *p*-(NO₂)C₆H₄CO₂H, toluene, –25 °C; (iii) K₂CO₃, MeOH; (b) (i) PhCONCO, THF; (ii) K₂CO₃, *n*-Bu₄NCl (0.2 equiv), MeCN, 0 °C; (c) NaOMe, MeOH; (d) (i) TBSCl, imidazole, DMF; (ii) NaH, MeI, DMF; (e) (i) BCl₃, CH₂Cl₂, –60 °C; (ii) TBSCl, imidazole, DMF; (f) (i) O₃, CH₂Cl₂–MeOH, –78 °C then Me₂S; (ii) (PhO)₂P(O)CH₂CO₂Et, NaH, THF, –78 to 0 °C; (g) 47% HF, MeCN, 70 °C then NaHCO₃.

followed by inversion¹⁰ of the hydroxy group gave enantiomerically pure **7** in 64% yield. Reaction of **7** with benzoyl isocyanate,¹¹ followed by treatment of the resulting *N*-benzoyl carbamate with K₂CO₃ allowed stereoselective cyclization accompanied by migration of the *N*-benzoyl group to afford cyclic carbamate **8** in 87% yield. Treatment of **8** with NaOMe in MeOH led to methanolysis of the benzoate and concomitant migration of the cyclic carbamate protecting group to give a 1:1 equilibrium mixture of **9** and **10**, quantitatively. These compounds were separated by silica gel column chromatography and **9** was treated with NaOMe in MeOH to convert it to the above-mentioned equilibrium mixture. As a result of this sequence, **10** was obtained in 75% yield from **8**. It is important to note that this sequence could be performed easily on large scale to provide multigram quantities of **10**. Silylation of **10** with *tert*-butyldimethylsilyl chloride and *N*-methylation of the product generated **11** in 80% yield. Removal of the benzyl

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* To whom correspondence should be addressed. Telephone: +81-95-847-1111 (ext. 2520). Fax: +81-95-848-4286. E-mail: susumi@net.nagasaki-u.ac.jp.

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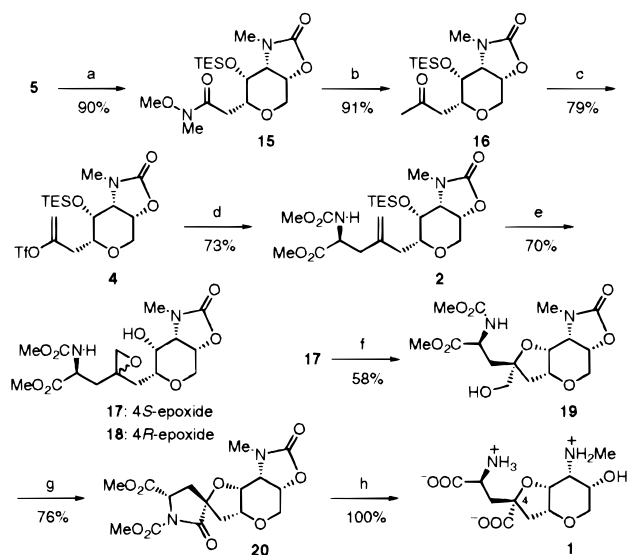
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Scheme 3^a

^a Reagents: (a) (i) MeONHMe·HCl, Me₂AlCl, CH₂Cl₂; (ii) TESCl, imidazole, DMF; (b) MeMgBr, THF, 0 °C; (c) LDA, 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, THF, -78 °C; (d) 3, (Ph₃P)₄Pd (10 mol %), LiCl (4 equiv), benzene–DMA–HMPA (20:1:1), 80 °C; (e) (i) 1 M HCl, THF; (ii) mCPBA, CH₂Cl₂; (f) (i) PPTS, acetone; (ii) NaOMe, MeOH; (g) n-Pr₄NRuO₄ (20 mol %), NMO, CH₂Cl₂; (h) 41% NaOH, reflux.

ethers with BCl₃, followed by silylation with *tert*-butyldimethylsilyl chloride gave a 4:1 mixture of 12 and 13 in 74% yield. Without separation, this mixture was subjected to ozonolysis and Horner-Emmons olefination using ethyl diphenylphosphonoacetate¹² to provide unsaturated ester 14 with complete Z-selectivity in 90% yield. Exposure of 14 to HF in acetonitrile led to formation of the corresponding butenolide which, upon basification with NaHCO₃, underwent intramolecular Michael addition of the primary hydroxy group to produce tricyclic lactone 5 as the sole product in 71% yield. Single-crystal X-ray analysis as well as NOE experiments secured the stereostructure of 5.

Having achieved construction of the *cis*-fused hexahydrofuro-[3,2-*b*]pyran core, we then proceeded to install the glutamic acid appendage (Scheme 3). Tricyclic lactone 5 was homologated to methyl ketone 16 via Weinreb amide 15 in 82% overall yield.¹³ Deprotonation of 16 with LDA, followed by triflation¹⁴ of the resulting lithium enolate with 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine allowed preferential formation of vinyl triflate 4 in 79% yield.¹⁵ To attach the alanine moiety to 4, the crucial palladium-catalyzed cross-coupling process was then investigated according to Jackson's protocol.⁵ After considerable experimentation, we eventually found the conditions where the desired cross-coupling took place cleanly. Thus, upon reaction of 4 with 3, prepared *in situ* from *N*-methoxycarbonyl-β-iodoalanine (5 equiv)¹⁶ by the action of Zn–Cu couple under sonication, in the presence of (PPh₃)₄Pd (10 mol %) and LiCl (4 equiv) in benzene–dimethylacetamide–HMPA (20:1:1) at 80 °C, coupling product 2 was obtained in 73% yield.

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(15) A 1:2 *E/Z*-mixture of the corresponding trisubstituted alkenyl triflates was also obtained in ~11% yield.

(16) Since methyl 2-(methoxycarbonylamino)acrylate was also formed under these conditions, the use of 3–5 equiv of *N*-methoxycarbonyl-β-iodoalanine was required for the sufficient production of the organozinc reagent.

With the advanced intermediate 2 in hand, the stage was set for completion of the total synthesis. Upon desilylation and epoxidation using mCPBA, 2 gave a 1:1 separable mixture of 4S-epoxide 17 and 4R-epoxide 18 in 70% yield. Treatment of 17 with PPTS (1 equiv) in acetone at room temperature, followed by methanolysis¹⁷ produced 19 in 58% yield. In this particular case, the cyclization turned out to take place with complete inversion of the stereochemistry of the quaternary center even though the reaction was very sluggish. Interestingly, when CSA was used in place of PPTS in CH₂Cl₂, the cyclization¹⁸ occurred with poor stereoselectivity to give a 3:2 mixture of 19 and its C4-epimer in 41% yield after methanolysis. It is important to note that 19 was also obtained from 4R-epoxide 18 by CSA catalyzed cyclization although the yield was moderate.¹⁹

Oxidation of 19 with TPAP-NMO²⁰ provided lactam 20 in 76% yield, the stereochemistry of which was confirmed via NOE experiments by comparison with the C4-epimer of 20 derived from 18. Finally, upon alkaline hydrolysis and neutralization using ion-exchange resin (IRC-76), 20 furnished (–)-dysiherbaine (1) which was purified by reverse-phase HPLC. The synthetic substance, [α]_D²⁴ –3.5° (c 0.23, H₂O), was identical with natural dysiherbaine, [α]_D²⁶ –3.5° (c 0.4, H₂O), by spectroscopic (¹H and ¹³C NMR)²¹ and chromatographic (reverse-phase TLC and HPLC) comparisons. 4-Epidysiherbaine was also synthesized from 18 in 45% overall yield in the same manner as that described for the synthesis of 1 from 17. The radioligand binding assay of synthetic 1 and 4-epidysiherbaine toward ionotropic glutamate receptors on rat brain synaptic membranes showed that synthetic 1 inhibited binding of [³H]-kainic acid and [³H]-1-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid to the same degree as that observed for natural dysiherbaine but 4-epidysiherbaine did not. These results further confirmed the absolute structure of natural dysiherbaine as depicted in 1.

In conclusion, we have achieved a total synthesis of (–)-dysiherbaine (1) from 6 in enantiocontrolled manner, thereby rigorously establishing its absolute structure. We demonstrated Jackson's cross-coupling methodology to be a powerful tool in the synthesis of highly functionalized amino acids for the first time. The synthetic route established herein should enable us to synthesize a variety of interesting analogues.

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Supporting Information Available: Experimental procedures, spectral data, and ¹H and ¹³C NMR spectra for new compounds, and tables of crystal data of 5 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) Since the corresponding δ-lactone was partially formed under the cyclization conditions, methanolysis was carried out to convert it to 19.

(18) This reaction possibly took place via a S_N1-like reaction process. However, it is also assumed that the cyclization occurred via a double inversion process involving participation of the carbamate group in competition with a S_N2-like reaction process because treatment of the *N*-Boc derivative of 17 with CSA in CH₂Cl₂ resulted in formation of the corresponding six-membered cyclic carbamate rather than the desired cyclization.

(19) The CSA catalyzed cyclization provided a 2:3 mixture of 19 and its C4-epimer in 51% yield, and the PPTS catalyzed cyclization gave the C4-epimer of 19 exclusively in 52% yield after methanolysis.

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