A highly stereocontrolled total synthesis of dysiherbaine†

Keisuke Takahashi, Takashi Matsumura, Jun Ishihara and Susumi Hatakeyama*

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A total synthesis of dysiherbaine, a potent agonist of AMPA-KA type glutamate receptors, has been accomplished in completely stereocontrolled manner starting from tri-*O*-acetyl-D-galactal in 25 steps and in 3% overall yield.

Dysiherbaine (**1**) and neodysiherbaine A (**2**) (Fig. 1), characteristic neuroexcitatory amino acids isolated from Micronesian sponge *Dysidea herbacea*,[1,2] are known to be subunit-selective agonists of AMPA-KA type glutamate receptors. These compounds exhibit the most potent convulsant activities among the excitatory amino acids known to date such as kainic acid and domoic acid.[3] Due to the low availability from natural sources as well as the intriguing biological activity and synthetically challenging molecular architectures, these compounds have attracted much attention in the chemical and biological communities.[4] Thus, there have been a number of synthetic studies including total syntheses of dysiherbaine (**1**) and neodysiherbaine A (**2**).[5–8] However, most of the syntheses are not efficient enough to obtain sufficient quantities of these natural products as well as their analogs, due to the lack of efficiency in the assembly of the *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system containing four contiguous all-*cis* stereogenic centres and one quaternary centre. Recently, in the synthesis of neodysiherbaine A (**2**),[7c] we successfully developed an efficient methodology for the stereocontrolled construction of the above-mentioned core structure. We herein report a new efficient synthesis of dyshiherbaine (**1**) based on the strategy we have established in the synthesis of neodysiherbaine A (**2**).

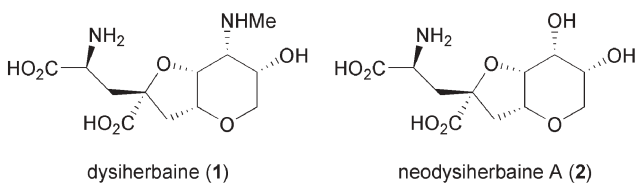
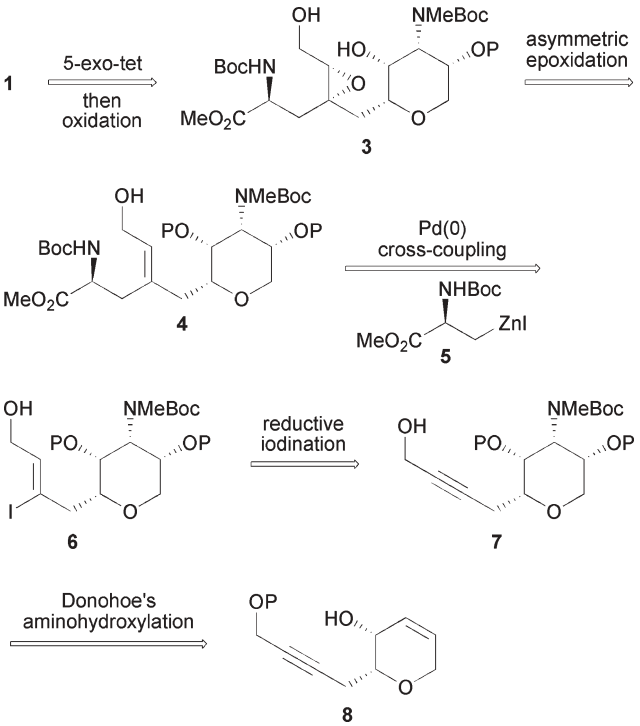


Fig. 1 Dysiherbaine and neodyshiherbaine A.

The synthetic route employed for the synthesis of **2** allowed us to envisage the retrosynthetic route consisting of 5-*exo-tet* cyclisation of epoxide **3** and cross-coupling[9] of organozinc compound **5** with alkenyl iodide **6**, accessible stereoselectively by reductive iodination[10] of **7**, as major transformations (Scheme 1). For the synthesis of **7**, we envisaged Donohoe's tethered intramolecular aminohydroxylation[11] of **8**, which was expected to be appropriate for the stereo- and regioselective construction of the three contiguous *cis* vicinal amino alcohol functionalities.‡



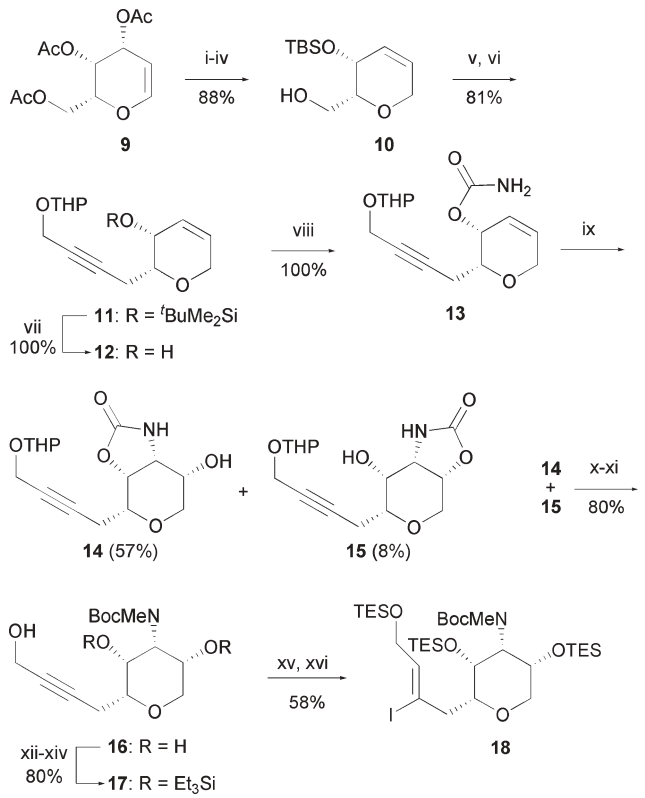
Scheme 1 Retrosynthetic analysis.

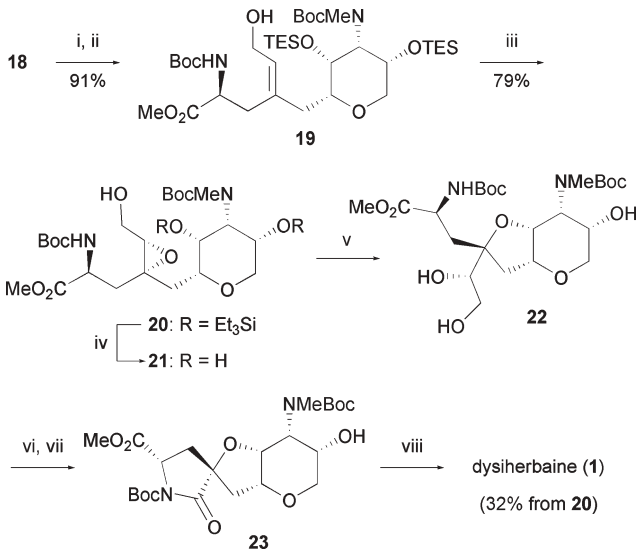
Our synthesis of **1** thus began with the preparation of allylic alcohol **12** (Scheme 2). Upon triethylsilane-promoted reduction, methanolysis, bis-silylation, and selective desilylation using NH_4F, tri-*O*-acetyl-D-galactal (**9**) was converted to alcohol **10** in good yield. According to Kotsuki's procedure,[12] **10** was triflated and the resulting triflate was then directly reacted with the lithium acetylide derived from propargyl tetrahydropyranyl ether to give **11**. Desilylation of **11** with TBAF furnished the required allylic alcohol **12** quantitatively.

After conversion of **12** to carbamate **13** by the addition of trichloroacetyl isocyanate, its tethered aminohydroxylation was investigated according to the procedures reported by Donohoe and co-workers.[11] Upon treatment of **13** with *tert*-butyl hypochlorite, NaOH, $K_2OsO_2(OH)_2$ and *i*-Pr_2NEt in aqueous *n*-propanol at room temperature, cyclic carbamate **14** and **15** were stereoselectively produced in 57 and 8% yields, respectively, together with recovered **13** (9%) (Scheme 3). Although the initially produced **14** isomerised partially to **15** through equilibration as mentioned above, this isomerisation was not a serious problem

Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, 852-8521, Japan. E-mail: susumi@nagasaki-u.ac.jp c; Fax: +81-95-819-2426; Tel: +81-95-819-2426

† Electronic supplementary information (ESI) available: Experimental details and selected ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b709627e





Scheme 2 *Reagents and conditions*. (i) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (ii) NaOMe, MeOH, rt; (iii) *t*-$BuMe_2SiCl$, imidazole, DMF, rt; (iv) NH_4F, MeOH, rt; (v) 2,6-lutidine, Tf_2O, CH_2Cl_2, −78 °C; (vi) *n*-BuLi, $THPOCH_2CCH$, DMPU, THF, −65 °C; (vii) *n*-Bu_4NF (TBAF), THF, rt; (viii) $CCl_3(CO)NCO$, CH_2Cl_2, 0 °C, then K_2CO_3, MeOH, rt; (ix) NaOH, *t*-BuOCl (1.06 eq.), *i*-Pr_2NEt (0.048 eq.), $K_2OsO_2(OH)_4$ (0.1 eq.), *n*-PrOH, rt; (x) 2-methoxypropene, PPTS (0.07 eq.), DMF–acetone (27:7), 0 °C; (xi) $LiAlH_4$, THF, 0 °C; (xi) conc. HCl, MeOH, reflux, then NaOH, Boc_2O, rt; (xii) Ac_2O, pyridine; (xiii) 2,6-lutidine, Et_3SiOTf, CH_2Cl_2, −78 °C; (xiv) K_2CO_3, MeOH, rt; (xv) $NaH_2Al(OCH_2CH_2OMe)_2$ (Red-Al), Et_2O, 0 °C, then I_2, −40 °C to rt; (xvi) Et_3SiCl, Et_3N, DMAP (0.1 eq.), CH_2Cl_2, rt.

Scheme 3 *Reagents and conditions*. (i) **5**, $(PPh_3)_4Pd$ (0.2 eq.), benzene, HMPA, dimethylacetamide, 80 °C; (ii) TBAF (0.9 eq.), AcOH (1.2 eq.), THF, rt; (iii) diisopropyl L-tartrate (0.1 eq.), Ti(O-*i*-Pr)$_4$ (0.09 eq.), *t*-BuOOH (2 eq.), 4A molecular sieves, CH_2Cl_2, −35 °C; (iv) TBAF (3 eq.), AcOH (4 eq.), THF, rt; (v) PPTS (1 eq.), CH_2Cl_2, rt; (vi) $NaIO_4$, THF-H_2O, rt; (vii) *n*-Pr_4NRuO_4 (TPAP) (0.2 eq.), *N*-methylmorpholine *N*-oxide (NMO) (2 eq.), 4A molecular sieves, MeCN, rt; (viii) 6 M HCl, 80 °C, neutralisation with NaOH.

because the mixture of **14** and **15** thus obtained was converted to a single advanced intermediate **16** by a three-step sequence involving temporary protection as the acetonide,§ $LiAlH_4$ reduction and acidic hydrolysis followed by *tert*-butoxycarbonylation. By successive acetylation, silylation and methanolysis, the secondary hydroxyl groups of **16** were protected as their triethylsilyl ethers to give **17**. Reaction[10] of **17** with Red-Al, followed by treatment of the resulting alkenylaluminate complex with iodine, allowed stereo- and regioselective formation of the corresponding (*Z*)-iodoalkene, which was then protected as its triethylsilyl ether to give **18**.

Having obtained key intermediate **18**, the final stage of our total synthesis was executed according to the methodology[7c] we have previously established. Thus, alkenyl iodide **18** was subjected to palladium-catalysed cross-coupling reaction with organozinc reagent **5**, generated from (*R*)-*N*-Boc-3-iodoalanine methyl ester, to furnish coupling product **19** very cleanly. Without purification, deprotection of **19** using TBAF in the presence of acetic acid gave alcohol **20** in excellent yield. Katsuki–Sharpless asymmetric epoxidation[13] using a catalytic amount of Ti(O-*i*-Pr)$_4$ and diisopropyl L-tartrate to afford epoxide **20** in perfect diastereoselectivity. In this epoxidation, the other diastereoisomeric epoxide was not detected. After removal of the triethylsilyl ether protecting groups of **20** using TBAF and acetic acid, the resulting triol **21** was successively subjected to acid-catalysed 5-*exo*-*tet* cyclisation, oxidative cleavage of the 1,2-glycol functionality and TPAP oxidation[14] to yield lactam **23**. In this transformation, the corresponding C4 epimer was not obtained at all, suggesting that the cyclisation occurred with complete inversion of stereochemistry at the quaternary centre. Finally, upon acidic hydrolysis and neutralisation with NaOH, **23** furnished dysiherbaine (**1**) which was purified by reverse-phase HPLC. The synthetic substance was identical with natural dysiherbaine by spectroscopic (^1H and ^{13}C NMR)¶ and chromatographic (reverse-phase TLC and HPLC) comparisons.

In conclusion, we have achieved an efficient synthesis of dysiherbaine (**1**) from tri-*O*-acetyl-D-galactal (**9**), which enables us to obtain this natural amino acid in sufficient quantities. The crucial assembly of the *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system containing four contiguous all-*cis* asymmetric centres and one quaternary centre was accomplished in completely stereocontrolled manner by the combination of Donohoe's tethered aminohydroxylation and our previously developed methodology involving palladium-catalysed cross-coupling and Katsuki–Sharpless epoxidation followed by 5-*exo*-*tet* cyclisation. The synthetic method is of general value in approaches to related neuroexcitatory amino acids.

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Notes and references

‡ Just recently, Cohen and Chamberlin[6e] reported an efficient synthesis of the tetrahydropyran core based on Donohoe's tethered aminohydroxylation; however, they have not synthesised dyshiherbaine.

§ Without this protection, the next $LiAlH_4$ reduction turned out to be unsuccessful to afford a complex mixture.

¶ In ^1H NMR (D_2O), chemical shifts of NCH_3 and C*H*NMe varied markedly depending on the concentration as we reported previously.[5a] However, the ^1H NMR (D_2O) spectrum of synthetic dysiherbaine hydrochloride was found to be completely identical with that of natural specimen.

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