Total Synthesis of (−)-Dysiherbaine

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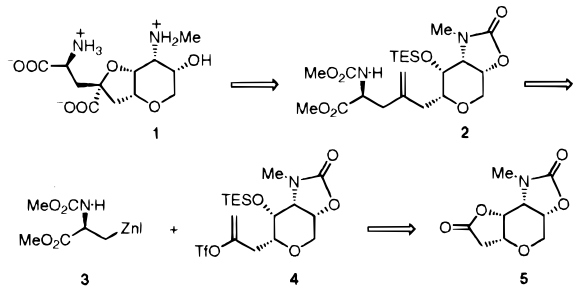
(−)-Dysiherbaine (**1**), a potent neuroexcitotoxin, was isolated by Sakai and co-workers from a Micronesian sponge *Dysidea herbacea* and found to be a selective agonist of non-NMDA (*N*-methyl-D-aspartate) type glutamate receptors in the central nervous system.[1] Structurally, this amino acid is characterized 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 synthesis[4] of (−)-dysiherbaine (**1**) in naturally occurring form.

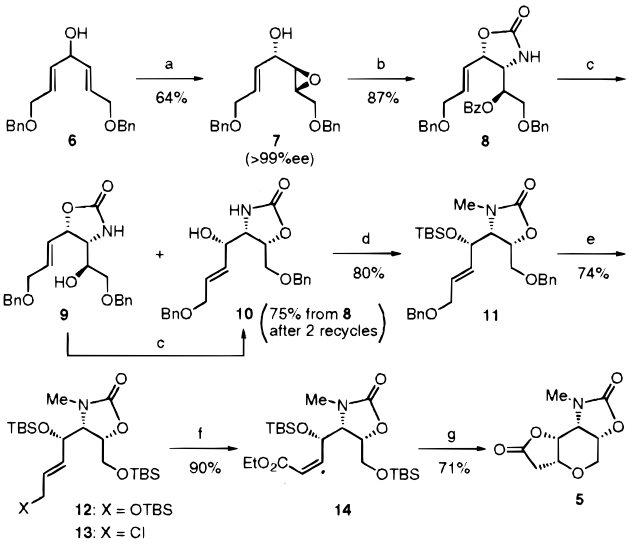
We envisaged tetra-substituted pyran **2** as a precursor of **1** and postulated that this intermediate could be accessed via palladium-catalyzed cross-coupling reaction of organozinc reagent **3** and vinyl triflate **4**, accessible from tricyclic lactone **5**, based on Jackson's protocol[5] (Scheme 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 developed[7] (Scheme 2). Thus, Katsuki−Sharpless catalytic asymmetric epoxidation[8,9] of **6**, followed by inversion[10] 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 K_2CO_3 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

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, CH_2Cl_2, −25 °C; (ii) DIPAD, Ph_3P, *p*-$(NO_2)C_6H_4CO_2H$, toluene, −25 °C; (iii) K_2CO_3, MeOH; (b) (i) PhCONCO, THF; (ii) K_2CO_3, *n*-Bu_4NCl (0.2 equiv), MeCN, 0 °C; (c) NaOMe, MeOH; (d) (i) TBSCl, imidazole, DMF; (ii) NaH, MeI, DMF; (e) (i) BCl_3, CH_2Cl_2, −60 °C; (ii) TBSCl, imidazole, DMF; (f) (i) O_3, CH_2Cl_2−MeOH, −78 °C then Me_2S; (ii) $(PhO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 to 0 °C; (g) 47% HF, MeCN, 70 °C then $NaHCO_3$.

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(1) Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112−4116.

(2) For the synthesis and biological activity of related model compounds, see: Sasaki, M.; Maruyama, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 3195−3198.

(3) For reviews on glutamate receptors, see: (a) Ozawa, S.; Kamiya, H.; Tsuzuki, K. *Prog. Neurobiol.* **1998**, *54*, 581−618. (b) Chittajallu, R.; Braithwaite, S. P.; Clarke, V. R. J.; Henley, J. M. *Trends Pharmacol. Sci.* **1999**, *20*, 26−35.

(4) (a) Masaki, H.; Maeyama, J.; Kamada, K.; Iwabuchi, Y.; Hatakeyama, S. In *41st Symposium on the Chemistry of Natural Products*, Symposium Papers; Nagoya; 1999; pp 13−18. (b) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635−638.

(5) (a) Jackson, R. F. W.; James, K.; Wythes, M. J.; Wood, A. *J. Chem. Soc., Chem. Commun.* **1989**, 644−645. (b) Jackson, R. F. W.; Wythes, M. J.; Wood, A. *Tetrahedron Lett.* **1989**, *30*, 5941−5944. (c) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397−3404. (d) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210−2215.

(6) For syntheses of amino acids using Jackson's methodology, see: (a) Ye, B.; Burke, T. R., Jr. *J. Org. Chem.* **1995**, *60*, 2640−2641. (b) Malan, C.; Morin, C. *Synlett* **1996**, 167−168. (c) Matsubara, J.; Otsubo, K.; Ohtani, S.; Kawano, Y.; Uchida, M. *Heterocycles* **1996**, *43*, 133−140. (d) Torisawa, Y.; Soe, T.; Katoh, C.; Motohashi, Y.; Nishida, A.; Hino, T.; Nakagawa, M. *Heterocycles* **1998**, *47*, 655−659.

(7) (a) Hatakeyama, S.; Satoh, K.; Takano, S. *Tetrahedron Lett.* **1993**, *34*, 7425−7428. (b) Hatakeyama, S.; Kojima, K.; Fukuyama, H.; Irie, H. *Chem. Lett.* **1995**, 763−764.

(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1987**, *109*, 5765−5780.

(9) For Katsuki-Sharpless asymmetric epoxidation of *σ*-symmetrical divinylcarbinols, see: (a) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201−5203 and references therein. (b) Jäger, V.; Schröter, D.; Koppenhoefer. *Tetrahedron* **1991**, *47*, 2195−2210 and references therein. (c) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793−4808 and references therein.

(10) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

(11) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776−777.

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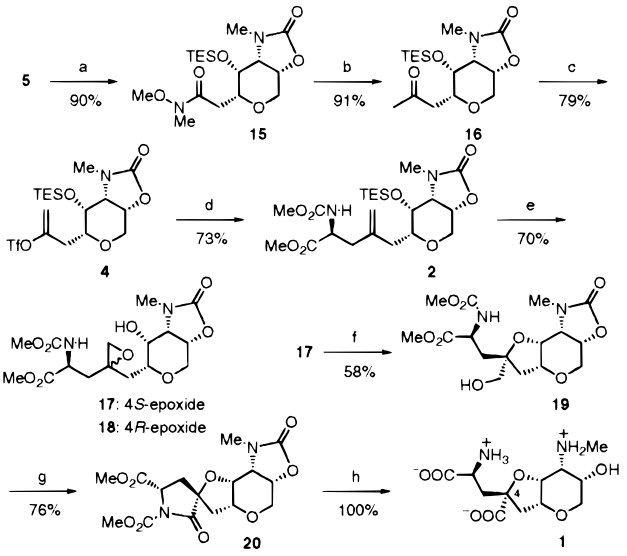
Scheme 3[a]



[a] Reagents: (a) (i) MeONHMe·HCl, Me_2AlCl, CH_2Cl_2; (ii) TESCl, imidazole, DMF; (b) MeMgBr, THF, 0 °C; (c) LDA, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, THF, −78 °C; (d) **3**, $(Ph_3P)_4Pd$ (10 mol %), LiCl (4 equiv), benzene−DMA−HMPA (20:1:1), 80 °C; (e) (i) 1 M HCl, THF; (ii) *m*CPBA, CH_2Cl_2; (f) (i) PPTS, acetone; (ii) NaOMe, MeOH; (g) *n*-Pr_4NRuO_4 (20 mol %), NMO, CH_2Cl_2; (h) 41% NaOH, reflux.

ethers with BCl_3, 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 diphenylphosphonoacetate[12] 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 $NaHCO_3$, 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 triflation[14] 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 $(PPh_3)_4Pd$ (10 mol %) and LiCl (4 equiv) in benzene−dimethylacetamide−HMPA (20:1:1) at 80 °C, coupling product **2** was obtained in 73% yield.

With the advanced intermediate **2** in hand, the stage was set for completion of the total synthesis. Upon desilylation and epoxidation using *m*CPBA, **2** gave a 1:1 separable mixture of 4*S*-epoxide **17** and 4*R*-epoxide **18** in 70% yield. Treatment of **17** with PPTS (1 equiv) in acetone at room temperature, followed by methanolysis[17] 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 CH_2Cl_2, the cyclization[18] 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 4*R*-epoxide **18** by CSA catalyzed cyclization although the yield was moderate.[19]

Oxidation of **19** with TPAP-NMO[20] 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, $[\alpha]^{24}_D$ −3.5° (*c* 0.23, H_2O), was identical with natural dysiherbaine, $[\alpha]^{26}_D$ −3.5° (*c* 0.4, H_2O), by spectroscopic (^1H and ^{13}C 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 [^{3}H]-kainic acid and [^{3}H]-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 ^{13}C 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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(12) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934−1939.

(13) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1991**, *22*, 3815−3818. (b) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685−2688.

(14) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(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.

(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 posssibly 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 CH_2Cl_2 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.

(20) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.

(21) In ^1H NMR spectra (D_2O), chemical shifts of NCH_3 and CH-NMe varied markedly depending on the concentration. However, the ^1H NMR spectrum (4.5×10^{-2} M DCl) of synthetic dysiherbaine was found to be completely identical with that of natural specimen.