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Total synthesis of (−)-dysiherbaine†

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The enantioselective synthesis of (−)-dysiherbaine (1) has been established with efficiency *via* a unique synthetic strategy involving the desymmetrization of 2-substituted glycerol to install a quaternary chiral carbon, which induces further stereochemistry in the bicyclic perhydrofuropyran through mercuriocyclization and epoxidation.

(−)-Dysiherbaine was isolated in 1997 by Sakai and his collaborators from extracts of the Micronesian marine sponge *Dysidea herbacea*.[1] Later, they corrected the original source as *Synechocystis cyanobacteria* harbored in the sponge *Lendenfeldia chondrodes*.[2] It has a characteristic molecular structure based on a *cis*-fused hexahydrofuro[3,2-*b*]pyran bicyclic core and a glutamate subunit with four contiguous stereogenic centers and a quaternary asymmetric carbon. Ligand binding assay studies revealed that dysiherbaine is a strong agonist of KA/AMPA type glutamate receptors pertaining to ionotropic glutamate receptors, which generate ligand-gated channels to convey fast excitatory synaptic transmission in the mammalian central nerve system.[3] Its binding to the receptors activates ion channels, disturbs ionic equilibria, and incurs glutamate excitotoxicity to cause neuronal overactivation and eventual cell death.[4] Dysiherbaine displays the most potent convulsant activity among the known excitatory amino acids such as domoic acid and kainic acid.[5] Since it induces epilepsy-like seizures in mice, it is considered in brain research as a potential surrogate of the current seizurogenic drugs.[6] Its beneficial pharmacological profiles and unique molecular architecture led us to be involved in synthetic studies on dysiherbaine. Furthermore, although many reports have been published concerning its synthesis, most of them are not practical enough to supply the scarce natural product.[7,8] Herein, we describe an asymmetric total synthesis of dysiherbaine with efficiency.

Our present retrosynthetic analysis of dysiherbaine (**1**) breaks the C–O bonds of the tetrahydropyranyl (THP) and tetrahydrofuranyl (THF) rings, and involves a diene alcohol intermediate **2** (Scheme 1). Conceivably, the intermediate evolves through mercurioetherification, with stereoselective uncertainty, and later acid-catalyzed cyclization *via* an epoxy alcohol to restore the THP and THF rings. The initial chiral invocation guides the fate of the remaining contiguous centers.

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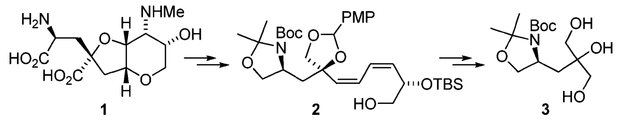
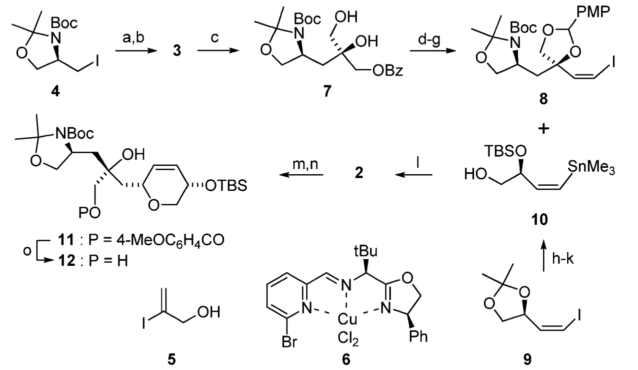


Scheme 1 Retrosynthetic analysis of (−)-dysiherbaine **1**. PMP = 4-methoxyphenyl, Boc = *tert*-butoxycarbonyl.

At the design stage, we assumed that (i) the tertiary allylic oxygen of **2** might exert an electrostatic stabilizing effect on the mercuronium cation and/or (ii) the allylic silyloxy group could sterically shield the α-face to favour the desired asymmetry in the 6-membered oxacycle. The construction of **2** was planned through Stille coupling with the vinyl iodide **8** and vinyltin **10**.[9] Recently, we developed an asymmetric desymmetrization of 2-substituted glycerols to enantioselectively form the corresponding tertiary alcohols.[10] The application of the desymmetrization protocol to the triol **3** was expected to install the required quaternary chiral carbon, which would be carried to the intermediate **2** through **8**.

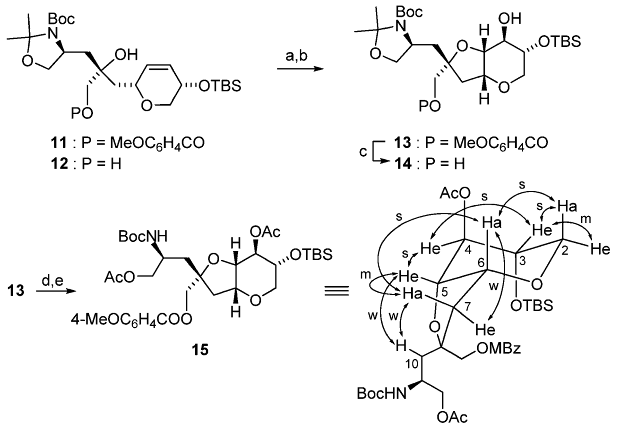
The synthesis of **1** commenced with preparation of **3**. After transmetallation of the commercial iodide **4**, the organozinc iodide generated was sonicated with the vinyl iodide **5** (readily derived from propargyl alcohol)[11] in the presence of Pd[12] to afford the coupled allylic alcohol in 87% yield (Scheme 2). The coupling reaction should be carried out at lower than 35 °C to suppress the decomposition of the organozinc iodide. The allylic alcohol was dihydroxylated to the triol **3**, and then benzoylated under established desymmetrization conditions using an imine monooxazoline–$CuCl_2$ catalyst **6**[10a] to furnish the predicted monobenzoate **7** with higher than 97% de in 96% yield. After the diastereomeric separation, **7** was sequentially converted into benzylidene acetals with 4-methoxybenzaldehyde dimethyl acetal, into alcohols by reduction ($LiAlH_4$), into aldehydes under Dess–Martin oxidation conditions,[13] and into vinyl iodides **8** with Stork's phosphonium salt[14] in 72% overall yield. All benzylidene acetal products were 1.5 : 1 diastereomeric mixtures. It is worthwhile to mention that while only the (*Z*)-iodoalkenes **8** could be detected with the crude aldehydes from the Dess–Martin oxidation in the olefination reaction, a 2–3 : 1 mixture of the (*Z*)- and (*E*)-geometric isomers were formed consistently with the chromatographically purified aldehydes. We supposed that the observed stereoselectivity difference would be attributed to the incompletely removed pyridine. Indeed, the Wittig olefination of the purified aldehydes generated the (*Z*)-stereoisomers exclusively in the presence of a few equivalents of pyridine. The production of vinyltin **10** as the Stille coupling partner[15] to **8** was initiated by the hydrolysis of the acetonide group of the known vinyl iodide **9**.



Scheme 2 Preparation of the dihydropyran **12**. (a) Zn–Cu, TMSCl, TMEDA, THF, sonication (150 W), RT, then **5**, $Pd(PPh_3)_4$, sonication (150 W), <35 °C, 87%. (b) OsO_4, NMO, H_2O, acetone, 0 °C, 99%. (c) **6**, BzCl, Et_3N, THF, RT, 95%. (d) PPTS, $PMPCH(OMe)_2$, PhH, RT, 97%. (e) $LiAlH_4$, Et_2O, 0 °C, 97%. (f) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C. (g) $ICH_2{}^+PPh_3I^-$, NaHMDS, HMPA, THF, −78 °C, 81% (over 2 steps). (h) 6N HCl, MeOH, RT, 95%. (i) TBSCl, DMAP, Et_3N, CH_2Cl_2, RT, 92%. (j) $(Me_3Sn)_2$, $Pd(PPh_3)_2Cl_2$, THF, RT, 90% (based on 10% recovered SM). (k) PPTS, MeOH, 0 °C, 88% (based on 15% recovered SM). (l) $Pd(PPh_3)_4$, CuI, CsF, DMF, RT, 85%. (m) $Hg(CF_3CO_2)_2$, K_2CO_3, PhMe, −30 °C, then Et_3B, $LiBH_4$, THF, −78 °C, 70%. (n) DDQ, 4A MS, PhH, RT. (o) K_2CO_3, MeOH, RT, 95% (over 2 steps). TMS = trimethylsilyl, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine, NMO = 4-methylmorpholine *N*-oxide, Bz = benzoyl, PPTS = pyridinium *p*-toluenesulfonate, HMDS = bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformamide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, MS = molecular sieves.

Subsequently, the two hydroxyl groups of the demasked diol were silylated, its iodo group was substituted by Pd-mediated stannylation,[15] and finally the primary silyloxy group was desilylated chemoselectively to offer **10** in 69% overall yield from **9**. Clean Stille coupling between **8** and **10** provided the diene alcohol **2** in 85% yield. Coupling using the corresponding tri-*n*-butyltin instead of the trimethyltin **10** was less effective (<20% yield) probably due to steric effects. Next, diastereoselective formation of the 6-membered heterocycle from **2** was needed, but involved a stereochemistry challenge. The survey of various electrophile-promoted cyclization conditions led us to resort to the one-pot process of mercuriocyclization followed by reductive demercuration.[16] Importantly, when this process was applied to **2**, the desired *cis*-3,6-disubstituted dihydropyran was produced in 70% yield, along with 1–2% of the *trans*-diastereomer. The acetals were cleaved with DDQ[17] to give a 20–25 : 1 mixture of primary benzoate **11** and tertiary benzoate, which was debenzoylated to the diol **12** in 95% overall yield. After separating the diastereomeric benzylidene acetals prepared from **7**, each diastereomer was also converted to **12**, respectively, as aforementioned; they were confirmed to have similar reactivity and stereoselectivity.

The bicyclic precursor **12** was exposed to NIS to give only the *cis*-fused hexahydrofuropyran in 90% yield. At this juncture, the intermolecular substitution reaction of the iodo group by the azide anion was attempted under various conditions. Also, after the removal of the TBS group, we intended to deliver the requisite nitrogen nucleophile intramolecularly through the secondary hydroxyl group. However, all trials proved unrewarding.

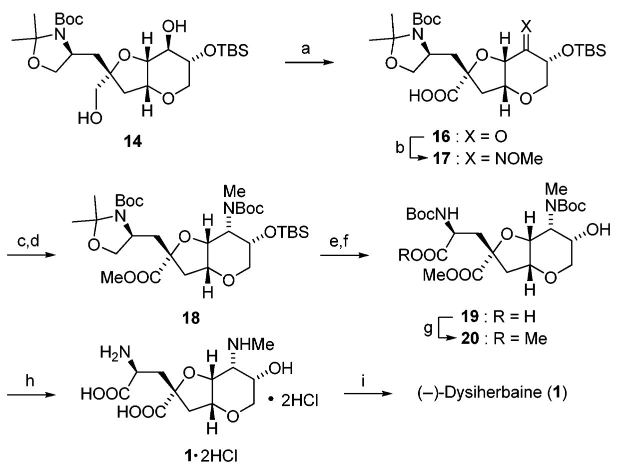


Scheme 3 Preparation of **14** and NOE measurement. (a) CF_3COCH_3, OXONE®, Na_2EDTA, $NaHCO_3$, MeCN, 0 °C. (b) $CDCl_3$, RT (87% for **12** to **14**, 75% for **11** to **13**). (c) K_2CO_3, MeOH, RT, 98%. (d) $InCl_3$, wet MeCN, RT, 95%. (e) Ac_2O, DMAP, Et_3N, CH_2Cl_2, RT, 100%. OXONE® = potassium peroxymonosulfate, EDTA = ethylenediaminetetraacetate, s = strong, m = medium, w = weak.

We contemplated introducing an oxygen instead of the iodo functional group. Accordingly, **12** was subjected to epoxidation using *m*CPBA, dimethyldioxirane and other peracids; it was found to be unreactive under mild conditions and decompose under harsh conditions. Eventually, the employment of trifluoromethylmethyldioxirane[18] allowed for the formation of the desired unstable epoxide, a portion of which (about 20%) was cyclized to the tetrahydrofuran derivative **14** under epoxidation conditions (Scheme 3). Treatment of this crude mixture with $CDCl_3$ gave the *cis*-fused bicyclic alcohol **14** as a single stereoisomer in 87% overall yield without any detection of the corresponding perhydropyranopyran. Its structure was manifested through conversion of the benzoate **11** to **14** *via* the bicyclic benzoate **13** *via* sequential epoxidation, cyclization and debenzoylation. In order to elucidate the stereochemistry of **14** at the ring junction, installed by the mercuriocyclization of **2** and epoxidation of **12**, several related derivatives were prepared for the purposes of discrete ^1H NMR spectral assignments that support its proposed three-dimensional structure. The bicyclic diacetate **15** gave adequate ^1H NMR peak separations: **11** was converted to **15** *via* **13**, in which the acetonide group was removed and acetylated. The NOE values of **15** were obtained to support the desired connectivity (Scheme 3). NOE signals between two H2s/H3, one H2/H6, H3/H4 and H4/H5 suggest a tetrahydropyran chair conformation; whereas H3 is positioned equatorially, H6 is situated axially. Since much stronger NOE crosspeaks were observed between H6/Ha7 than were for H6/He7, H6 and Ha7 are assigned to be in the same face of the tetrahydrofuran ring. Also, crosspeaks for Ha7/H10, H5/H10 and H5/Ha7 support that H5, H6, Ha7 and the C10 side chain occupy the β-face of the 5-membered heterocycle. Spectroscopically, it is concluded that **14** is a *cis*-fused bicyclic compound with a *cis* relationship between C3 and C6 (Scheme 3). The stereochemical arrangement of **14** was also confirmed by synthesizing the known dimethyl ester **20** as well as (−)-dysiherbaine **1** (*vide infra*).

The remaining synthetic issue is the critical installation of the 4-amino functionality. In this context, **14** was oxidized to the unstable keto carboxylic acid **16**[19] before being converted to the oxime **17**[20] in 88% overall yield. Due to its relative instability, it was immediately hydrogenated in the presence of Boc_2O; the resulting unstable carbamate carboxylic acid was methylated to give **18** in 81% overall yield. The appended acetonide, silyl and *t*-butoxycarbonyl groups are plausible factors for the instability of all the carboxylic acid derivatives, due to their acidic lability. The acidic hydrolysis of **18** followed by the chemoselective oxidation of the primary hydroxyl group of the generated diol gave the stable carboxylic acid **19** in 95% overall yield, which was confirmed downstream upon its conversion to the corresponding known methyl ester **20**.[7d] It is noted that under identical deprotection conditions, only the acetonide group was removed from **13**, whereas both the acetonide and silyl groups were removed from **18**. Finally, the global acidic deprotection of **19** produced the dysiherbaine hydrochloride **1**·2HCl quantitatively, which was briefly treated with aqueous NaOH and then purified on an ion exchange resin to afford (−)-dysiherbaine **1** in 95% yield. The ^1H NMR spectral data of **1**·2HCl are highly dependent on sample concentration, and are similar to that reported by Snider and Hawryluk (0.005 M)[7a] and by Hatakeyama *et al.* (0.03 M).[7c] While its optical rotation is known to be $[\alpha]_D = -5°$ (*c* 0.06, H_2O) by Snider and Hawryluk[7a] and $[\alpha]_D^{23} = +7.0°$ (*c* 0.53, H_2O) by Hatakeyama *et al.*,[7f] our value is $[\alpha]_D^{23} = +7.0°$ (*c* 0.54, H_2O). In the case of (−)-dysiherbaine **1**, the ^1H NMR spectra are almost identical with those previously published,[7c,d,f] its optical rotation found by us, $[\alpha]_D^{24} = -7.3°$ (*c* 0.38, H_2O), is in good agreement with the reported value, $[\alpha]_D^{23} = -7.5°$ (*c* 0.52, H_2O) by Hatakeyama *et al.*, (Scheme 4).[7f]

We report an efficient asymmetric total synthesis of (−)-dysiherbaine from the readily available chiral building block **4**. The synthesis has demonstrated the utility of the enantioselective desymmetrization of the 2-substituted glycerol **3** to install a quaternary chiral center, which is thought to guide further stereoselectivity in the formation of the bicyclic perhydro-furanopyran.



Scheme 4 Preparation of dysiherbaine **1**. (a) AZADO, $PhI(OAc)_2$, $NaClO_2$, pH 6.2 phosphate buffer, MeCN, RT. (b) $MeONH_2$·HCl, pyridine, 0 °C to RT, 88% (over 2 steps). (c) H_2 (1 atm), Boc_2O, $NaHCO_3$, Raney Ni, MeOH, RT. (d) NaH, MeI, DMF, 0 °C, 81% (over 2 steps). (e) $InCl_3$, wet MeCN, RT (96%). (f) AZADO, $PhI(OAc)_2$, $NaClO_2$, pH 5.8 phosphate buffer, MeCN, RT, 99%. (g) $TMSCHN_2$, MeOH, PhH, RT, 100%. (h) 6 M HCl, 80 °C, 99%. (i) 10 M aq NaOH, RT, then Amberlite, weakly acidic cation exchanger, H form, 95%. AZADO = 2-azaadamantane *N*-oxyl.

Other significant operations in the synthetic sequence include Stille coupling of **8** and **10**, the stereoselective mercuriocyclization of **2**, and the successful epoxidation of the unreactive alkene **12**.

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Notes and references

1 R. Sakai, H. Kamiya, M. Murata and K. Shimamoto, *J. Am. Chem. Soc.*, 1997, **119**, 4112.
2 R. Sakai, K. Yoshida, A. Kimura, K. Koike, M. Jimbo, K. Koike, A. Kobiyama and H. Kamiya, *ChemBioChem*, 2008, **9**, 543.
3 (*a*) R. Dingledine, K. Borges, D. Bowie and S. F. Trynelis, *Pharmacol. Rev.*, 1999, **51**, 7; (*b*) D. R. Madden, *Nat. Rev. Neurosci.*, 2002, **3**, 91; (*c*) G. T. Swanson, T. Green, R. Sakai, A. Contractor, W. Che, H. Kamiya and S. F. Heinemann, *Neuron*, 2002, **34**, 589; (*d*) M. L. Mayer, *Curr. Opin. Neurobiol.*, 2005, **15**, 282; (*e*) J. M. Sanders, K. Ito, L. Settimo, O. T. Pentikainen, M. Shoji, M. Sasaki, M. S. Johnson, R. Sakai and G. T. Swanson, *J. Pharmacol. Exp. Ther.*, 2005, **314**, 1068; (*f*) M. L. Mayer, *Nature*, 2006, **440**, 456.
4 J. M. Sanders, O. T. Pentikainen, L. Settimo, U. Pentikainen, M. Shoji, M. Sasaki, R. Sakai, M. S. Johnson and G. T. Swanson, *Mol. Pharmacol.*, 2006, **69**, 1849.
5 R. Sakai, G. T. Swanson, M. Sasaki, K. Shimamoto and H. Kamiya, *Cent. Nerv. Syst. Agents Med. Chem.*, 2006, **6**, 83.
6 R. Sakai, G. T. Swanson, K. Shimamoto, A. Contractor, A. Ghetti, Y. Tamura-Horikawa, C. Oiwa and H. Kamiya, *J. Pharmacol. Exp. Ther.*, 2001, **296**, 650.
7 Total syntheses: (*a*) B. B. Snider and N. A. Hawryluk, *Org. Lett.*, 2000, **2**, 635; (*b*) M. Sasaki, T. Koike, R. Sakai and K. Tachibana, *Tetrahedron Lett.*, 2000, **41**, 3923; (*c*) H. Masaki, J. Maeyama, K. Kamada, T. Esumi, Y. Iwabuchi and S. Hatakeyama, *J. Am. Chem. Soc.*, 2000, **122**, 5216; (*d*) D. Phillips and A. R. Chamberlin, *J. Org. Chem.*, 2002, **67**, 3194; (*e*) M. Sasaki, N. Akiyama, K. Tsubone, M. Shoji, M. Oikawa and R. Sakai, *Tetrahedron Lett.*, 2007, **48**, 5697; (*f*) K. Takahashi, T. Matsumura, J. Ishihara and S. Hatakeyama, *Chem. Commun.*, 2007, 4158; (*g*) M. Sasaki, K. Tsubone, K. Aoki, N. Akiyama, M. Shoji, M. Oikawa, R. Sakai and K. Shimamoto, *J. Org. Chem.*, 2008, **73**, 264.
8 Formal and partial syntheses: (*a*) T. Naito, J. S. Nair, A. Nishiki, K. Yamashita and T. Kiguchi, *Heterocycles*, 2000, **53**, 2611; (*b*) S. H. Kang and Y. M. Lee, *Synlett*, 2003, 993; (*c*) O. Miyata, R. Iba, J. Hashimoto and T. Naito, *Org. Biomol. Chem.*, 2003, **1**, 772; (*d*) J. Huang, K. Xu and T. Loh, *Synthesis*, 2003, 755; (*e*) J. L. Cohen, A. Limon, R. Miledi and A. R. Chamberlin, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2189; (*f*) W. R. F. Goundry, V. Lee and J. E. Baldwin, *Synlett*, 2006, 2407; (*g*) J. L. Cohen and A. R. Chamberlin, *Tetrahedron Lett.*, 2007, **48**, 2533; (*h*) R. Fernandez de la Pradilla, N. Lwoff and A. Viso, *Tetrahedron Lett.*, 2007, **48**, 8141; (*i*) C. L. Carroll and A. R. Chamberlin, *Tetrahedron Lett.*, 2011, **52**, 3995.
9 S. P. H. Mee, V. Lee and J. E. Baldwin, *Angew. Chem.*, 2004, **116**, 1152.
10 (*a*) B. Jung and S. H. Kang, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 1471; (*b*) B. Jung, M. S. Hong and S. H. Kang, *Angew. Chem., Int. Ed.*, 2007, **46**, 2616.
11 N. Kamiya, Y. Chikami and Y. Ishii, *Synlett*, 1990, 675.
12 G.-Q. Shi, X.-H. Huang and F. Hong, *J. Org. Chem.*, 1996, **61**, 3200.
13 M. J. Batchelor, R. J. Gillespie, J. M. C. Golec and C. J. R. Hedgecock, *Tetrahedron Lett.*, 1993, **34**, 167.
14 K. Zhao and G. Stork, *Tetrahedron Lett.*, 1989, **30**, 2173.
15 J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Koewn, C. S. N. Kolz and B. W. Phillips, *J. Org. Chem.*, 2002, **67**, 7750.
16 S. H. Kang, J. H. Lee and S. B. Lee, *Tetrahedron Lett.*, 1998, **39**, 59.
17 Z. Zhang and G. Magnusson, *J. Org. Chem.*, 1996, **61**, 2394.
18 D. Yang, M.-K. Wong and Y.-C. Yip, *J. Org. Chem.*, 1995, **60**, 3887.
19 (*a*) M. Shibuya, M. Tomizawa, I. Suzuki and Y. Iwabuchi, *J. Am. Chem. Soc.*, 2006, **128**, 8412; (*b*) M. Inai, T. Goto, T. Furuta, T. Wakimoto and T. Kan, *Tetrahedron: Asymmetry*, 2008, **19**, 2771.
20 O. Miyata, R. Iba, J. Hashimoto and T. Naito, *Org. Biomol. Chem.*, 2003, **1**, 772.