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 Symcheocystis cyanobacteria harbored in the sponge Lendenfeldia chondrodes. 2 It has a characteristic molecular structure based on a cis-fused hexahydropyro[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, 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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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 10 13 to furnish the predicted monobenzoate 7 with higher than 97% de in 96% yield. After the diastereomeric separation, 7 was sequentially converted into benzylicene 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 benzylicene 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 acetone group of the known vinyl iodide 9.
Subsequently, the two hydroxyl groups of the demasked diol were silylated, its iodo group was substituted by Pd-mediated stannylation, and finally the primary silyloxy group was desilylated chemoselectively to offer the desired connectivity (Scheme 3). NOE signals between two protons in the diol, each diastereomer was confirmed to have similar reactivity and stereoselectivity.

We contemplated introducing an oxygen instead of the iodo functional group. Accordingly, 12 was subjected to epoxidation using mCPBA, dimethylidioxirane and other peracids; it was found to be unreactive under mild conditions and decompose under harsh conditions. Eventually, the employment of trifluoromethylmethylidioxirane 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 CDCl₃ gave the cis-fused bicyclic alcohol 14 as a single stereoisomer in 87% overall yield without any detection of the corresponding perhydrofuranopyran. Its structure was manifested through conversion of the benzoate 11 to 14 via the bicyclic benzoate 13 via sequential epoxidation, cyclization and debenzylation. 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 tetrahydrofuran chair conformation; whereas H3 is positioned equatorially, H6 is situated axially. Since much stronger NOE crosspeaks were observed between H6/H7 than were for H6/H7, H6 and H7 are assigned to be in the same face of the tetrahydrofuran ring. Also, crosspeaks for H5/H10, H5/H10 and H5/H7 support that H5, H6, H7 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 (−)-dysiberaine 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 before being converted...
to the oxime 17 in 88% overall yield. Due to its relative instability, it was immediately hydrogenated in the presence of Boc₂O; the resulting unstable 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. 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 23 in 95% yield.

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

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Notes and references