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Synthesis of (−)-Dysiherbaine

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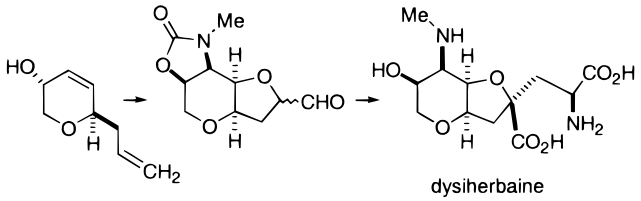
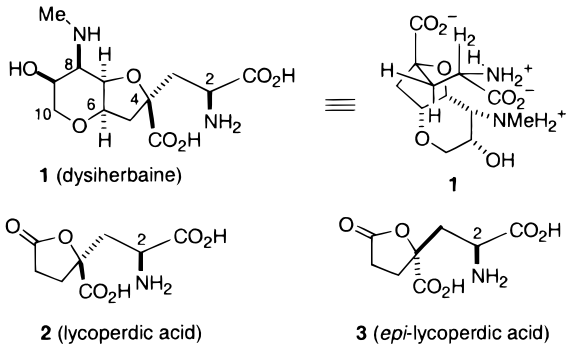
ABSTRACT



dysiherbaine

The first synthesis of (−)-dysiherbaine has been accomplished using intramolecular S_N2 substitutions of a carbamate anion on an epoxide and an alkoxide on a secondary mesylate to efficiently construct the bicyclic skeleton stereospecifically from xylose. A general sequence has been developed to introduce an allyl group and convert it to the alanine side chain that should be useful for the construction of dysiherbaine analogues.

(−)-Dysiherbaine (**1**) is a novel neurotoxic amino acid isolated from the Micronesian marine sponge *Dysidea herbacea* by Sakai and co-workers in 1997.[1] It is a potent neurotoxin reminiscent of domic acid that appears to function as an agonist for non-NMDA type glutamate receptors in the central nervous system. The structure of dysiherbaine was assigned on the basis of one- and two-dimensional NMR studies. The relative configuration of the bicyclic portion was determined by coupling constant analysis and NOE studies. The relative stereochemistry at C_2 was determined by careful analysis of proton−proton and proton−carbon coupling constants, which suggested that **1** exists preferentially in the conformation with intramolecular hydrogen bonding between the basic tetrahydrofuran oxygen and the ammonium group, giving rise to coupling constants for H_2 of 11.5 and 2.5 Hz. This assignment is supported by comparison to lycoperdic acid (**2**), in which H_2 absorbs as a dd, J = 10.3, 3.3 Hz, while in the diastereomer **3** H_2 absorbs as a dd, J = 5.9, 5.1 Hz.[2] The absolute stereochemistry of dysiherbaine was not determined but is most likely as shown with *S* stereochemistry at C_2, since non-NMDA type glutamate receptors bind preferentially to *S* amino acids.[3]



1 (dysiherbaine) ≡ **1**

2 (lycoperdic acid) **3** (*epi*-lycoperdic acid)

The potent biological activity and structural novelty of dysiherbaine prompted us to undertake its synthesis. Dysiherbaine contains six chiral centers on a novel bicyclic skeleton, making it a challenging synthetic target. The polarity of the molecule vastly increases the synthetic challenge since suitable protecting groups must be chosen to make the intermediates sufficiently lipophilic that they can be separated from inorganic reagents and purified chromatographically.

We envisioned that the three-carbon side chain of **1** could be introduced stereospecifically by alkylation of ester **4** from the less hindered α-face as shown in Scheme 1. Ester **4**

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

(2) Yoshifuji, S.; Kaname, M. *Chem. Pharm. Bull.* **1995**, *43*, 1617−1620.

(3) Watkins, J. C.; Krogsgaard-Larsen, P.; Honoré, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25−33.

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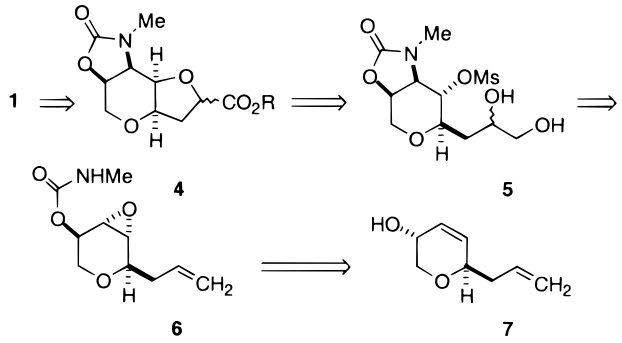
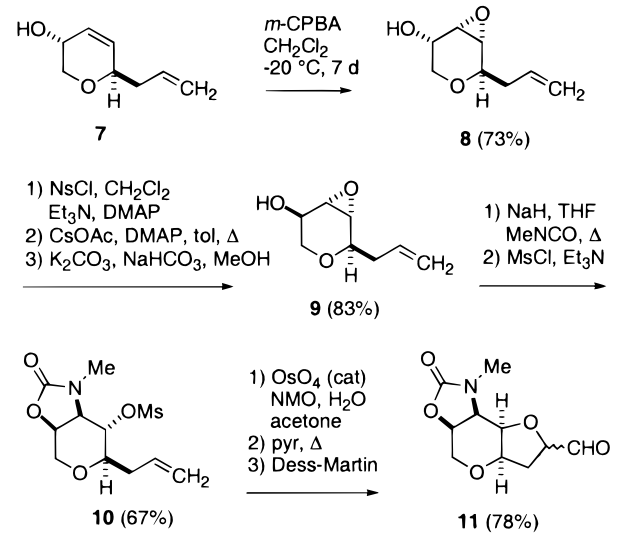
Scheme 1



should be readily available from diol mesylate **5**, which should undergo an intramolecular S_N2 reaction regiospecifically to give the tetrahydrofuran rather than the tetrahydropyran.[4] Mesylate **5** can be prepared by Roush's procedure involving attack of the carbamate anion on the epoxide of **6**.[5] Epoxide **6** can be prepared from allylic alcohol **7**, which has been prepared from diacetyl-L-xylal by reaction with allyltrimethylsilane and $TiCl_4$.[6] This approach should be useful for the preparation of analogues since both enantiomers of xylose are readily available.

Hydroxy-directed epoxidation of **7** with *m*-CPBA in CH_2Cl_2 for 7 d at −20 °C afforded 73% of epoxide **8**, 15% of the bis epoxide, and 8% of recovered **7** (Scheme 2). More

Scheme 2

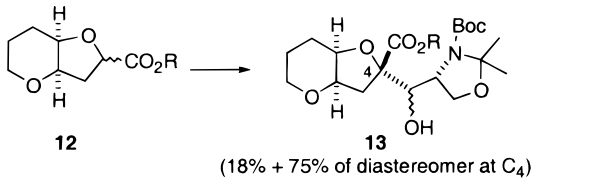


bis epoxide was formed at higher temperatures. Hydroxy-directed epoxidation with $VO(acac)_2$ and *t*-BuOOH gave mixtures containing mainly enone. The hydroxy group of **8** was now inverted by conversion to the nosylate with nosyl chloride, DMAP, and Et_3N in CH_2Cl_2 at 0 °C. Displacement of the nosylate with CsOAc and DMAP in toluene at reflux for 8 h and hydrolysis of the acetate with K_2CO_3 and $NaHCO_3$ in MeOH at room temperature for 1 h gave **9** in 83% yield from **8**. Use of $NaHCO_3$ as a buffer was necessary to prevent Payne rearrangement of the epoxy alcohol.

Reaction of **9** with NaH and methyl isocyanate in THF by Roush's procedure[5] afforded the oxazolidinone alcohol, which was treated with MsCl and Et_3N in CH_2Cl_2 to form mesylate **10** in 67% yield from **9**. Dihydroxylation with OsO_4 and NMO afforded a mixture of diols that was heated in pyridine at reflux for 4 h to form the tetrahydrofuran ring.[4] Dess−Martin oxidation gave aldehydes **11** as a 2:1 mixture of diastereomers in 78% yield from **10**. The mixture of isomers is of no consequence since the stereocenter will be set during the introduction of the three-carbon side chain. The formation of aldehydes in the Dess−Martin oxidation establishes unambiguously that the intramolecular S_N2 reaction gave only tetrahydrofuranmethanols since oxidation of a tetrahydropyranol would have given a ketone, not an aldehyde.

Having prepared the fully functionalized bicyclic framework efficiently and stereospecifically, we turned our attention to the introduction of the three-carbon side chain. While this work was in progress, Sasaki and Tachibana reported the synthesis of a dysiherbaine model lacking the hydroxy and methylamino groups.[7] Their route proceeded through an aldol reaction with the enolate of **12**, which, surprisingly, gave only 18% of the desired diastereomer **13** and 75% of the diastereomer in which the aldehyde reacted with the enolate from the β face, which had been expected to be more hindered (Scheme 3). This was cause for concern, although

Scheme 3



we anticipated that the presence of the oxazolidinone in **11** would improve selectivity for the desired isomer.

Model studies for the attachment of the side chain were carried out with 2-tetrahydrofurancarboxylic acid. Since initial attempts at allylation of the ester enolate proceeded in low yield, we turned our attention to the Ireland Claisen rearrangement.[8] Reaction of allyl ester **14** with LDA and TMSCl/Et_3N afforded 94% of Claisen rearrangement product **15**, which was converted to the primary amide by reaction

(4) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863−5868.

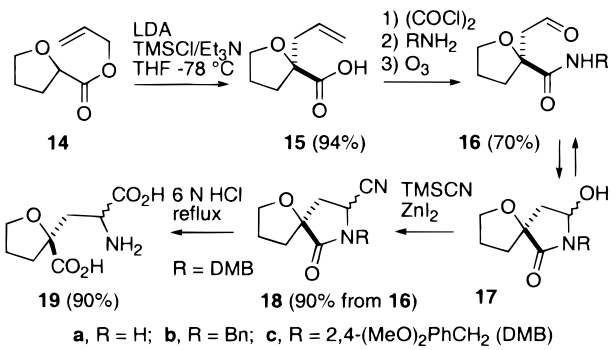
(5) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752−3757.

(6) (a) Sabol, J. S.; Cregge, R. J. *Tetrahedron Lett.* **1989**, *30*, 6271−6274. (b) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917−1920.

(7) Sasaki, M.; Maruyama, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 3195−3198.

(8) (a) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279−3285. (b) Di Florio, R.; Rizzacasa, M. A. *J. Org. Chem.* **1998**, *63*, 8595−8598.

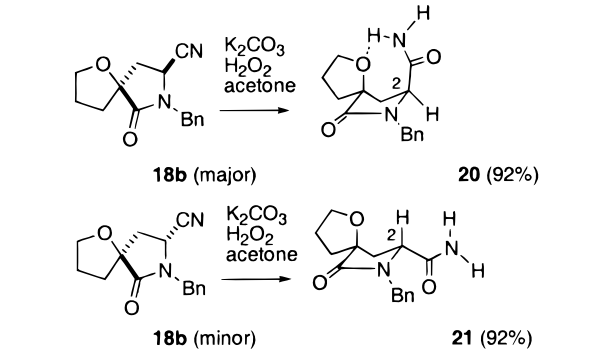
Scheme 4



with oxalyl chloride and then ammonia (Scheme 4). Ozonolysis gave aldehyde **16a**, which was treated with base to give an equilibrium 1:1 mixture of lactam alcohol **17a** and amide aldehyde **16a**. We prepared a secondary amide to increase the lipophilicity and with the hope that it would form a lactam alcohol more readily than the primary amide. Benzyl amide **16b** was prepared in 70% yield from **15** analogously to the preparation of **16a** with the expectation that it could be cleaved hydrogenolytically at the end of the synthesis. We were delighted to find that treatment of **16b** with K_2CO_3 afforded lactam alcohol **17b** quantitatively. Treatment of **17b** with ZnI_2 and TMSCN[9] afforded cyano lactam **18b** as a separable 2:1 mixture of isomers in 90% yield.

Mild hydrolysis of the major and minor nitriles **18b** with basic hydrogen peroxide afforded amides **20** and **21**, respectively (Scheme 5) in 92% yield. The structure of the

Scheme 5

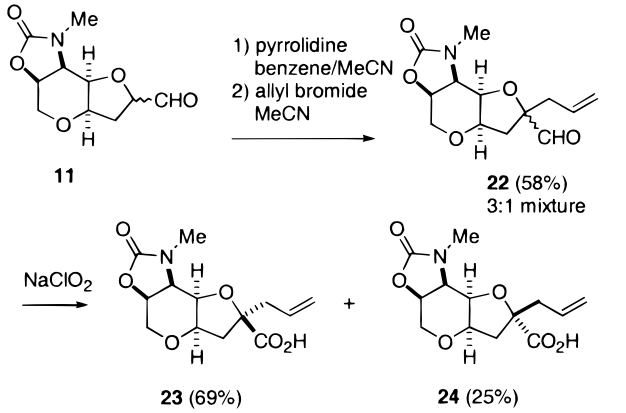


desired major diastereomer **20**, which has the same relative stereochemistry as **1**, was established by examination of its NMR spectrum. The amide hydrogens of **20** absorb at δ 5.46 and 6.91. The downfield shift of the hydrogen at δ 6.91 is indicative of an intramolecular hydrogen bond to the tetrahydrofuran ring.[10] H_2 absorbs as a dd, J = 8.4, 1.8 Hz, as calculated by MM2 for the conformation shown. The amide hydrogens of **21** absorb at δ 5.79 and 5.84, which indicates that they are not hydrogen bonded. H_2 absorbs as a dd, J = 8.4, 4.4 Hz, as calculated by MM2 for the conformation shown.

Unfortunately, benzyl lactams **18b**, **20**, or **21** could not be hydrolyzed,[11] although *N*-unsubstituted lactams can be hydrolyzed with HCl. Since hydrogenolysis of benzyl lactams is not possible, we replaced the benzyl group with a 2,4-dimethoxybenzyl group, which should be cleaved by the acidic hydrolysis conditions needed to hydrolyze the nitrile and lactam.[12] Nitriles **18c** were prepared analogously to that of **18b** using 2,4-dimethoxybenzylamine. We were delighted to find that reaction of **18c** in 6 M HCl at reflux for 2 d afforded the desired amino acids **19** in 90% yield, thereby providing a protocol that should be suitable for conversion of **11** to dysiherbaine.

Initial attempts at the Ireland Claisen rearrangement of the allyl ester obtained from **11** proceeded in low yield, possibly due to interference by the oxazolidinone. Fortunately, a Claisen variant reported by Secrist for allylation of carbohydrate aldehydes was successful.[13] Reaction of the pyrrolidine enamine of **11** with allyl bromide in acetonitrile at room temperature to 80 °C afforded 58% of an inseparable 3:1 mixture of aldehydes **22** after hydrolysis of the iminium salt (Scheme 6). Oxidation of **22** with $NaClO_2$ afforded 69%

Scheme 6

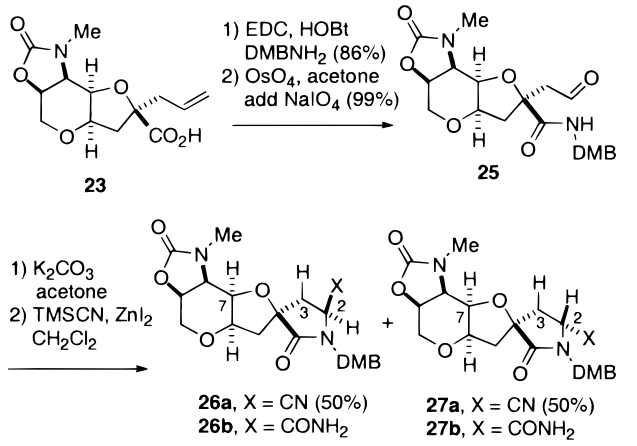


of acid **23** and 24% of the undesired diastereomer **24**, which were easily separated chromatographically. The structures were tentatively assigned on the basis of the chromatographic behavior. The desired major product **23** was substantially less polar [**23**, R_f = 0.34; **24**, R_f = 0.14 (77:23 EtOAc/MeOH)] since the acid group of **23** is on the more hindered concave face and is intramolecularly hydrogen bonded to the tetrahydropyran oxygen.

(9) Tung, R. D.; Rich, D. H. *Tetrahedron Lett.* **1987**, *28*, 1139−1142.
(10) Boiadjiev, S. E.; Person, R. V.; Lightner, D. A. *Tetrahedron: Asymmetry* **1993**, *4*, 491−510.
(11) For a similar observation see: Ohta, T.; Shiokawa, S.; Sakamoto, R.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 7329−7332.
(12) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777−1778.
(13) Secrist, J. A., III.; Winter, W. J., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2554−2555.

The 2,4-dimethoxybenzyl amide was introduced in 86% yield by reaction of **23** with EDC, HOBt, and 2,4-dimethoxybenzylamine in wet MeCN (Scheme 7). Cleavage

Scheme 7

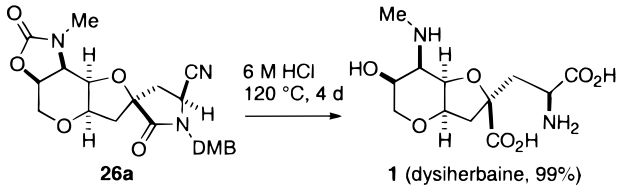


of the double bond with OsO_4 and then $NaIO_4$ provided 99% of aldehyde **25**.[14] Cyclization with K_2CO_3 in wet acetone afforded 99% of the lactam alcohols, which were treated with TMSCN and ZnI_2 in CH_2Cl_2 to provide 99% of a 1:1 mixture of readily separable nitriles **26a** and **27a**.

The stereochemistry at C_4 was confirmed by the NOEs between H_3 and H_7 in both **26a** and **27a**. The stereochemistry at C_2 was established by analysis of the ^{1}H NMR spectra of amides **26b** and **27b**, which were prepared by hydrolysis of the nitriles with H_2O_2 and K_2CO_3 in acetone, as described above for **20** and **21**. The amide hydrogens of the desired isomer **26b** absorb at δ 5.33 and 6.10, indicating the presence of an intramolecular hydrogen bond. H_2 absorbs as a dd, J = 9.2, <1 Hz. The amide hydrogens of the diastereomer **27b** absorb at δ 5.32 and 5.65; H_2 absorbs as a dd, J = 7.6, 5.6 Hz. The coupling constants of both **26b** and **27b** correspond closely to those calculated by MM2 and observed in model amides **20** and **21**.

The final step in the synthesis was hydrolysis with 6 M HCl at reflux, which was expected to hydrolyze the oxazolidinone,[15] hydrolyze the nitrile to an acid, cleave the dimethoxybenzyl group, and hydrolyze the resulting N-unsubstituted lactam. We were delighted to find that reaction of nitrile **26a** in 6 M HCl for 4 d at reflux, concentration under reduced pressure, and washing the residue with CH_2Cl_2 to remove byproducts from the dimethoxybenzyl group afforded dysiherbaine **1** cleanly as the hydrochloride salt (Scheme 8). Although the natural product is the free amino

Scheme 8



acid, the ^{1}H and ^{13}C NMR spectral data of the synthetic material are identical to those of an authentic sample kindly provided by Prof. Sakai.[16] The rotation, $[\alpha]^{25}_D$ −5°, corresponds closely to that of the natural product, $[\alpha]^{25}_D$ −3°. This suggests that the absolute configuration of dysiherbaine is as shown, although the small magnitude of the rotation and the possibility of pH effects on the rotation preclude definitive assignment.

In conclusion, we have completed the first synthesis of dysiherbaine using intramolecular S_N2 substitutions of a carbamate anion on an epoxide and an alkoxide on a secondary mesylate to efficiently construct the bicyclic skeleton stereospecifically from L-xylose. A general sequence that should be useful for the construction of dysiherbaine analogues has been developed to introduce an allyl group and convert it to the alanine side chain. Preparation and biological evaluation of the stereoisomers at C_2 and C_4 are in progress.

Acknowledgment. We are grateful to the National Institutes of Health (GM-46470) for generous financial support. We thank Ms. Christine Hofstetter for assistance in obtaining NMR spectra and Professor Sakai for an authentic sample of dysiherbaine.

Supporting Information Available: Experimental procedures for the preparation of **8**−**11**, **22**−**27**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Ozone oxidized the electron rich aromatic ring.

(15) Knapp, S.; Sebastian, M. J.; Ramanathan, H. *J. Org. Chem.* **1983**, *48*, 4786−4788.

(16) The pH of a dilute solution of **1** (1 mg/mL) in D_2O may be controlled by dissolved CO_2.