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Total Synthesis of (−)- and (+)-Dysibetaine

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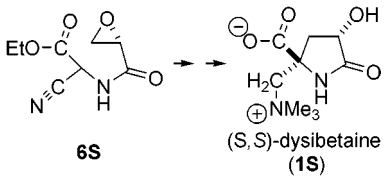
ABSTRACT



Glycidamides 6R and 6S were elaborated to (*R*,*R*)- and (*S*,*S*)-dysibetaines (1R and 1S) by intramolecular alkylation and functional group modification in 23% overall yield. The absolute stereochemistry of natural dysibetaine was established as *S*,*S* by comparison of the optical rotation of the natural product with that of the synthetic materials.

Sakai and co-workers recently reported the isolation of (−)-dysibetaine (**1**) from an aqueous extract of the marine sponge *Dysidea herbacea* collected in Yap, Micronesia (see Figure 1).[1] The structure was determined by spectroscopic

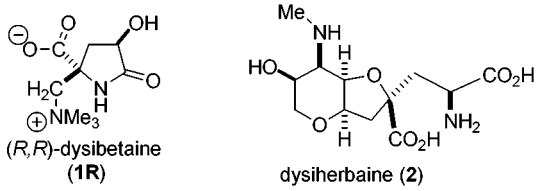


Figure 1. Dysibetaine and dysiherbaine.

methods and X-ray crystallography. The absolute stereochemistry was not assigned. Intracerebral injection of **1** in mice (20 μg/mouse) induced scratching, suggesting that dysibetaine may have some activity toward glutamate receptors in the central nervous system. The same group had previously reported the isolation from the same sponge of the potent non-NMDA type glutamate receptor agonist dysiherbaine (**2**),[2] which has been the subject of intense synthetic interest.[3]

We report here the first synthesis of dysibetaine (**1**) using the intramolecular alkylation of a glycidamide to construct the pyrrolidinone ring and the assignment of the (*S*,*S*) stereochemistry to the natural product. Retrosynthetic analysis suggested that (*R*,*R*)-dysibetaine (**1R**) might be accessible by selective modification of the esters of **3R**, which could be prepared by intramolecular alkylation of glycidamide **4R** (see Scheme 1).[4] Alternatively, **1R** could be prepared by reduction of the nitrile of **5R** and methylation of the resulting amine. Nitrile ester **5R** should be available by intramolecular alkylation[4] of glycidamide **6R**. Since the former route required selective modification of a diester and the latter route was likely to give a mixture of isomers in the alkylation step, both sequences were examined.

(1) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941−6944.

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

(3) (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635−638. (b) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216−5217. (c) Sasaki, M.; Koike, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 3923−3926.

(4) For related reactions, see: (a) Funaki, I.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 9909−9924. (b) Wang, J.-q.; Tian, W.-s. *J. Chem. Soc., Perkin Trans. 1* **1996**, 209−212. (c) Huang, D.-F.; Huang, L. *Tetrahedron* **1990**, *46*, 3135−3142. (d) Shiozaki, M.; Ishida, N.; Hiroaka, T.; Maruyama, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2135−2139.

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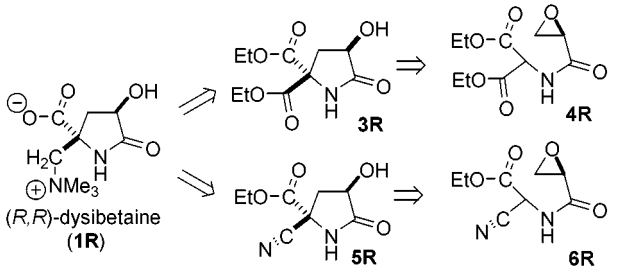
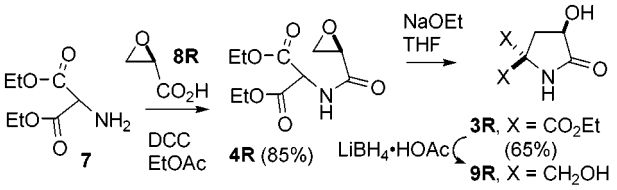
Scheme 1. Retrosynthetic Analysis for (*R*,*R*)-Dysibetaine (**1R**)



Reaction of diethyl aminomalonate (**7**), (*R*)-glycidic acid (**8R**),[5] and DCC in EtOAc for 1 h at 0 °C and 12 h at room temperature afforded 85% of glycidamide **4R** (see Scheme 2). Intramolecular alkylation with NaOEt in THF gave

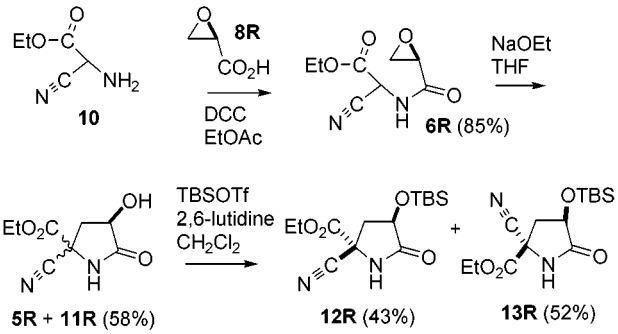
Scheme 2. Preparation of Diester **3R** and Diol **9R**



65% of pyrrolidinone **3R**. Although reduction of **3R** with $LiBH_4$·HOAc[6] cleanly provided diol **9R**, we were unable to selectively reduce either ester of **3R**. We therefore examined the cyclization of cyanoacetate **6R**.

Reaction of ethyl amino(cyano)acetate (**10**),[7] (*R*)-glycidic acid (**8R**),[5] and DCC in EtOAc for 1 h at 0 °C and 12 h at room temperature gave 85% of glycidamide **6R** (see Scheme 3). Intramolecular alkylation was effected by adding 0.15

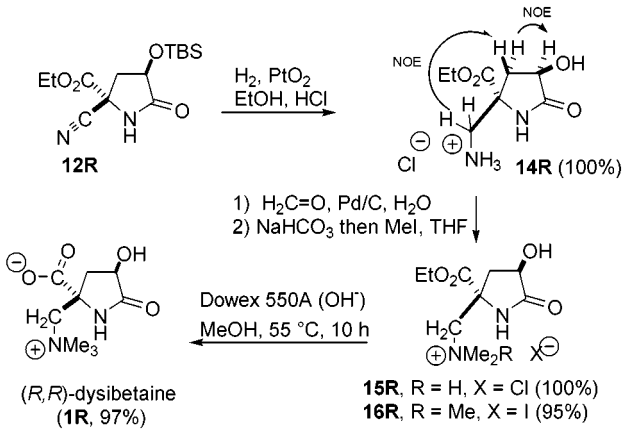
Scheme 3. Preparation of **5R** and **11R**



equiv of 1.58 M NaOEt in EtOH to a 0.02 M solution of **6R** in THF and heating the resulting solution at 60 °C for 24 h to give 8% of recovered **6R** and 58% of a difficultly separable 45:55 mixture of **5R** and **11R**, whose stereochemistry was established by NOE studies on **14R** and **17R** (see below). Reaction of the mixture with TBSOTf and 2,6-lutidine in CH_2Cl_2 gave the easily separated TBS ethers. Flash chromatography afforded 43% of the desired silyl ether **12R** and 52% of the diastereomer **13R**.

Hydrogenation of the nitrile over Pd, Rh, or Ni was not clean. Fortunately, hydrogenation[8] of **12R** over PtO_2 in ethanol containing 3−4 equiv of concentrated HCl cleaved the silyl ether and reduced the nitrile, affording a quantitative yield of hydroxy amine hydrochloride **14R** on filtration and concentration of the reaction mixture (see Scheme 4). The

Scheme 4. Preparation of (*R*,*R*)-Dysibetaine (**1R**)



stereochemistry was established by NOE experiments, which showed cross-peaks between the ring methylene proton at δ 1.95 and the aminomethyl protons at δ 3.38−3.34 and between the other ring methylene proton at δ 2.77 and the methine proton at δ 4.44.

Clarke−Eschweiler methylation[9] of **14R** with aqueous CH_2O and Pd/C under 50 psi of H_2 gave ammonium salt **15R** in quantitative yield. Neutralization with $NaHCO_3$ and reaction of the tertiary amine with excess MeI in THF at room temperature for 36 h afforded 95% of trimethylammonium iodide **16R**. Hydrolysis of **16R** with Dowex 550A in the hydroxide form[10] in MeOH at 55 °C for 10 h followed by filtration and concentration provided 97% of pure (*R*,*R*)-dysibetaine (**1R**).[11] The ^1H and ^{13}C NMR spectra are

(5) Prepared from (*S*)-serine: Peterson, B. S.; Roush, W. S. *Org. Synth.* **1998**, *75*, 37−44.

(6) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131−6141.

(7) (a) Heitsch, H.; Wagner, A.; Yadav-Bhatnagar, N.; Griffoul-Marteau, C. *Synthesis* **1996**, 1325−1330. (b) Ahn, H.-S.; Bercovici, A.; Boykow, G.; Bronnenkant, A.; Chackalamannil, S.; Chow, J.; Cleven, R.; Cook, J.; Czarniecki, M.; Domalski, C.; Fawzi, A.; Green, M.; Gündes, A.; Ho, G.; Laudicina, M.; Lindo, N.; Ma, K.; Manna, M.; McKittrick, B.; Mirzai, B.; Nechuta, T.; Neustadt, B.; Puchalski, C.; Pula, K.; Silverman, L.; Smith, E.; Stamford, A.; Tedesco, R. P.; Tsai, H.; Tulshian, D.; Vaccaro, H.; Watkins, R. W.; Weng, X.; Witkowski, J. T.; Xia, Y.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 2196−2210.

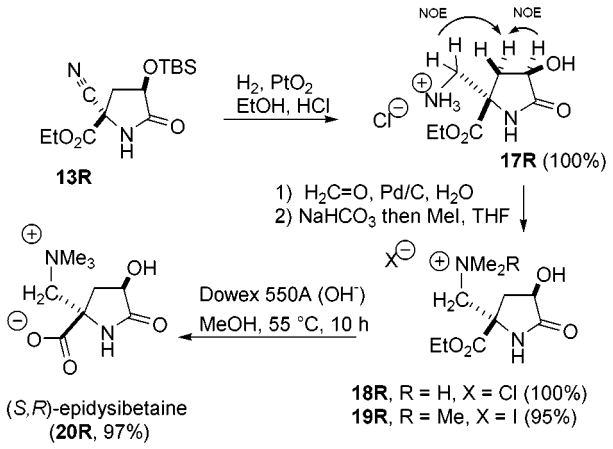
(8) (a) Brouilette, W. J.; Saeed, A.; Abuelyaman, A.; Hutchison, T. L.; Wolkowicz, P. E.; McMilin, J. B. *J. Org. Chem.* **1994**, *59*, 4297−4303. (b) Vergne, F.; Aitken, D. J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 6071−6075.

(9) (a) Xu, J.; Yadan, J. C. *J. Org. Chem.* **1995**, *60*, 6296−6301. (b) Reinhold, V. N.; Ishikawa, Y.; Melville, D. B. *J. Med. Chem.* **1968**, *11*, 258−260.

identical to those reported except that the quaternary carbon absorbs at δ 64.1, not 66.0.[12] The optical rotation, $[\alpha]_D = +5.3°$, is similar in magnitude but opposite in sign to that reported for the natural product, $[\alpha]_D = -7.3°$, indicating that the natural product is (*S*,*S*)-dysibetaine (**1S**).

An analogous series of reactions converted **13R** to epidysibetaine (**20R**) (see Scheme 5). Hydrogenation of **13R**

Scheme 5. Preparation of (*S*,*R*)-Epidysibetaine (**20R**)



over PtO_2 in ethanol containing 3−4 equiv of concentrated HCl gave a quantitative yield of hydroxy amine hydrochloride **17R** on filtration and concentration of the reaction mixture. The stereochemistry was established by NOE experiments, which showed cross-peaks between the ring methylene proton at δ 2.56 and both the methine proton at δ 4.38 and the aminomethyl protons at δ 3.35 and δ 3.21. There were no NOEs between the other ring methylene proton at δ 2.17 and either the aminomethyl or methine protons.

(10) Dowex 550A resin (5 g) in a column was washed with 20% aqueous NaOH (100 mL) and then H_2O (25 mL) to make sure that it was fully in the hydroxide form. This resin was heated in CH_3OH (25 mL) at 60 °C for 24 h to remove any MeOH soluble impurities and cooled to room temperature. The resin was filtered, washed with MeOH, and dried in air before use.

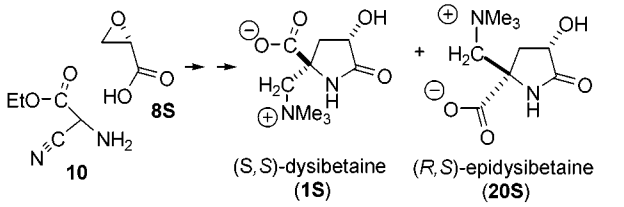
(11) **1R**: ^{1}H NMR (D_2O, HOD at δ 4.65, 20.0 °C) 4.21 (dd, 1, J = 8.0, 5.5), 3.90 (d, 1, J = 14.0), 3.60 (d, 1, J = 14.0), 3.07 (s, 9), 2.53 (dd, 1, J = 13.9, 8.0), 1.86 (dd, 1, J = 13.9, 5.5); ^{13}C NMR (D_2O, CD_3OD at δ 49.0 as internal standard) 179.5, 176.8, 73.1, 69.1, 64.1, 55.6 (3 C), 42.4; IR 3361, 1713, 1626; $[\alpha]_D = +5.3$ (c = 0.26, H_2O); HRMS (FAB) calcd for $C_9H_{16}N_2O_4$ (MH^+) 217.1188, found, 217.1190.

(12) The reported value of δ 66.0 is a typographical error. The natural product absorbs at δ 64.1: Prof. Ryuchi Sakai, private communication, April 5, 2001.

Clark−Eschweiler methylation of **17R** (100%), neutralization of **18R** with $NaHCO_3$ and reaction of the tertiary amine with excess MeI (95%), and hydrolysis of **19R** with Dowex 550A in the hydroxide form in MeOH at 55 °C for 10 h provided 97% of pure (*S*,*R*)-epidysibetaine (**20R**) with spectral data quite different from those of dysibetaine (**1R**).[13]

An identical sequence of reactions was used to prepare natural (*S*,*S*)-dysibetaine (**1S**) and (*R*,*S*)-epidysibetaine (**20S**) from ethyl amino(cyano)acetate (**10**) and (*S*)-glycidic acid (**8S**), which is readily available from (*R*)-serine (see Scheme 6).[5] The optical rotation of synthetic **1S**, $[\alpha]_D = -7.1°$, is

Scheme 6. Preparation of (*S*,*S*)-Dysibetaine (**1S**) and (*R*,*S*)-Epidysibetaine (**20S**)



very close to that reported for the natural product, $[\alpha]_D = -7.3°$.[1]

In conclusion, we have developed a seven-step synthesis of (−)-dysibetaine (**1S**), which proceeds in 20% overall yield and establishes the absolute stereochemistry of the natural product. The key step is the intramolecular alkylation of glycidamide **6**, which provides a mixture of **5** and **11** containing the fully functionalized pyrrolidinone of dysibetaine. This sequence makes dysibetaine (**1S**) and its three stereoisomers, **1R**, **20R**, and **20S**, readily available for further biological evaluation.

Acknowledgment. We are grateful to the NIH for generous financial support (GM-46470). We thank Prof. Sakai for copies of the spectra of natural dysibetaine.

Supporting Information Available: Experimental details and NMR spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) **20R**: ^{1}H NMR (D_2O, HOD at δ 4.65, 19.2 °C) 4.42 (dd, 1, J = 9.8, 7.9), 3.90 (d, 1, J = 14.0), 3.45 (d, 1, J = 14.0), 3.02 (s, 9), 2.46 (dd, 1, J = 13.4, 7.9), 1.90 (dd, 1, J = 13.4, 9.8); ^{13}C NMR (D_2O, CD_3OD at δ 49.0 as internal standard) 179.2, 176.8, 71.6, 68.6, 62.0, 55.4 (3 C), 43.1; $[\alpha]_D = +9.5$ (c = 0.30, CH_3OH).