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Diastereoselective Syntheses of Deoxydysibetaine, Dysibetaine, and Its 4-Epimer

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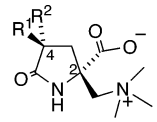
(±)-Deoxydysibetaine **2** and 4-*epi*-dysibetaine **3** were prepared in a few steps from methyl pyroglutamate through a regioselective Mannich reaction at C-2. Natural (2*S*,4*S*)-dysibetaine **1**, a sponge metabolite isolated from *Dysidea herbacea*, and (2*S*)-**2** were synthesized from enantiopure (*S*)-pyroglutaminol with very high stereoselectivity. The key steps were an original formation of stereogenic quaternary center C-2 and the diastereoselective hydroxylation at C-4.

Introduction

Synthetic studies of natural products of marine origin are still the focus of great interest due to their scarcity and their potential biological activities.[1] As part of our contribution in this field,[2] we envisioned the synthesis of dysibetaine **1**, a sponge metabolite isolated in 1999 from *Dysidea herbacea* collected in Yap (Micronesia). As dysibetaine is able to induce convulsive behavior in mice, this compound was suspected of acting to glutamate receptors in the central nervous system.[3]

Results and Discussion

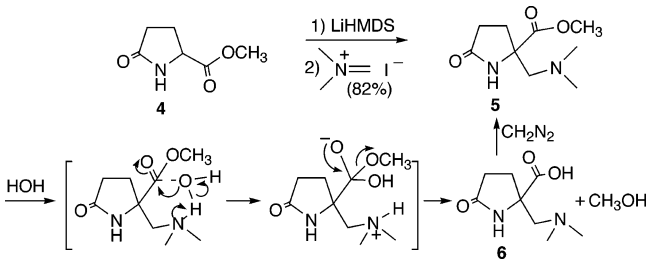
Before the achievement of this work, only one total synthesis of dysibetaine has been described by Snider et al., assigning its absolute configuration.[4a] A second synthesis, involving a nitrenium ion cyclization, has been reported very recently.[4b] This lactam can be considered as a cyclized α,γ-disubstituted glutamic acid, and the α-substitution by a trimethylammoniummethyl group constitutes an original structural feature. The introduction of a dimethylaminomethyl substituent as precursor of this functional group, starting either from methyl pyroglutamate **4** or enantiopure (*S*)-pyroglutaminol, represented our first target to give access to deoxydysibetaine **2**.



1: R^1 = OH, R^2 = H
2: R^1 = R^2 = H
3: R^1 = H, R^2 = OH

Racemic Methyl 2-*N*,*N*-Dimethylaminomethylpyroglutamate from Methyl Pyroglutamate 4. Starting from methyl pyroglutamate **4**, a direct addition at C-2 of dimethyliminium iodide (Eschenmoser's salt) seemed the simplest route to add a *N*,*N*-dimethylaminomethyl group at C-2. The regioselective deprotonation of pyroglutamates at C-2 or C-4 depends on the absence, or not, of an electrowithdrawing *N*-protecting group. Thus, *N*-alkoxycarbonyl groups direct the addition of electrophiles at C-4, and such a regioselectivity in the addition of Eschenmoser's salt has already been verified in our laboratory.[5] Accordingly, methyl pyroglutamate was directly deprotonated at C-2 with LiHMDS (2.1 equiv) without being *N*-protected and was alkylated with Eschenmoser's salt at − 60 °C providing **5** in 82% yield (Scheme 1).[6] The isolation of **5** however was rather difficult and needed a rapid extraction, due to the unstability of the methyl ester function. Indeed, this ester is particularly sensitive to water and rapidly hydrolyzed at room temperature with the assistance of the neighboring amino group, to give **6** as outlined in the Scheme 1. This hydrolysis was responsible of decreased yields when prolonged isolation stages occurred, but the compound **5** could be recovered by treatment of **6** with diazomethane.

SCHEME 1



Such a participation of the nitrogen lone pair in a hydrolysis process has been already observed with the acetate of vindoline.[7] Moreover, the corresponding salts of **5** (hydrochloride or trifluoroacetate) proved to be stable.

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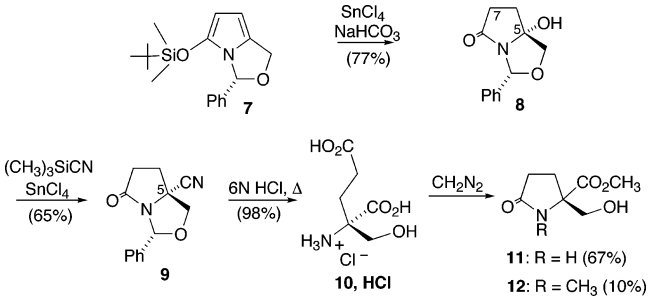
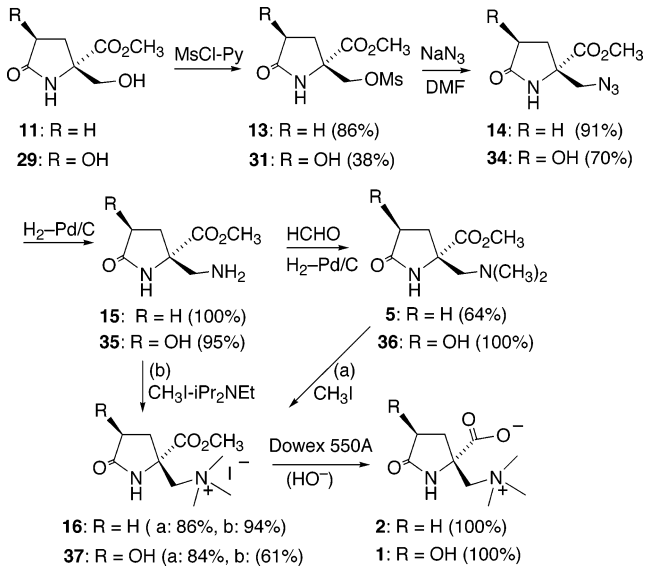
SCHEME 2



Enantiopure (*S*)-Methyl 2-*N*,*N*-Dimethylaminomethylpyroglutamate (*S*)-5 from (*S*)-Pyroglutaminol. With racemic intermediate **5** in hand, the route to its enantiopure counterpart (*S*)-**5** was investigated from (*S*)-methyl 2-hydroxymethylpyroglutamate **11**.[6,8] This ester was derived from (*S*)-2-hydroxymethylglutamic acid hydrochloride **(10**, **HCl)**,[9,10] efficiently and stereoselectively prepared from the bicyclic silyloxypyrrole **7**,[11,12] according to Scheme 2. The stable 5-hydroxy derivative **8** was easily obtained in 77% yield by successive treatment of silyloxypyrrole **7** with Lewis acid such as $SnCl_4$ and then with aqueous sodium bicarbonate solution. Starting from **7**, this nucleophilic addition of hydroxide anion at C-5 is equivalent to a double protonation at C-7 and C-6 followed by trapping the resulting iminium ion with the nucleophile. The entire process probably took place upon quenching of the reaction mixture with aqueous alkaline solution, leading to a slow hydrolysis of the complex between silyloxypyrrole **7** and $SnCl_4$.[10] The diastereoselectivity of this nucleophilic addition was complete, with an attack of the iminium ion on the face hindered by the phenyl group at C-2, and this was confirmed by X-ray crystal analysis of **8**.[13] Other nucleophiles could replace the hydroxyl group of **8** under similar conditions. A cyano group was introduced at C-5 by means of trimethylsilylcyanide in the presence of $SnCl_4$, affording **9**. Only one diastereomer was detected and was isolated in 65% yield.[12] Acidic hydrolysis of **9** gave rise to (*S*)-2-hydroxymethyl glutamic acid **10, HCl** (98%), which was methylated with trimethylsilyldiazomethane or with an excess of diazomethane in ether and cyclized in the same step into (*S*)-methyl 2-hydroxymethylpyroglutamate **11** (67%), along with some *N*-methyl derivative **12** (~10%). The presence of methanol as cosolvent to increase the solubility of the diacid could explain this *N*-methylation.[14]

(*S*)-Methyl 2-hydroxymethylpyroglutamate **11** was converted into (*S*)-methyl 2-*N*,*N*-dimethylaminomethylpyroglutamate (*S*)-**5** following Scheme 3. Primary amine **15** was obtained in 78% overall yield through mesylate **13** and azidomethyl derivative **14**. *N*-Dimethylation with aqueous formaldehyde under hydrogen furnished (*S*)-**5** (64%).

SCHEME 3



Deoxydysibetaine 2. Both racemic **5** and (*S*)-**5** led to the corresponding trimethylammonium iodides **16** in good yields (86%), by classical reaction with iodomethane, as shown in the Scheme 3 for the (*S*)-enantiomer, and **16** afforded deoxydysibetaine **2** by treatment with resin Dowex 550A (HO^- form, 85−100%), according to the protocol described by Snider et al.[4a] Trimethylammonium iodide (*S*)-**16** was also obtained more efficiently (94%) by direct trimethylation of the primary amine **14** with iodomethane in excess in the presence of diisopropylethylamine. This more direct route avoided the isolation of the labile compound (*S*)-**5**.

Natural Dysibetaine 1. The synthesis of dysibetaine **1** involved a hydroxylation step at C-4. Several electrophilic reagents were tested to introduce this hydroxyl group in the α-position of lactam−carbonyl through enolates. For this purpose, (*S*)-methyl *2*-hydroxymethyl pyroglutamate **11** was monoprotected as *O*-TBDMS (**17**, 100%) and then *N*-protected as *tert*-butyl carbamate (**18**, 91%). The reaction of potassium enolate of **18** with oxygen gas[15] failed to provide any hydroxylated compound in the presence of trimethyl phosphite. Dibenzyl peroxydicarbonate[16,17] has been previously described to oxidize *N*-Boc-*O*-TBDMS pyroglutaminol, affording the corresponding benzyloxycarbonyloxy derivative in 50% yield and high diastereoselecivity.[18] As potassium enolates were reported to give better results than lithium analogues,[17] the derivative **18** was deprotonated with KHMDS at −78 °C and treated with $(BnOCOO)_2$. Surprisingly, two diastereomers **19** and **20** were isolated in only 34% yield and low stereoselectivity (dr 2.4:1, Scheme 4).

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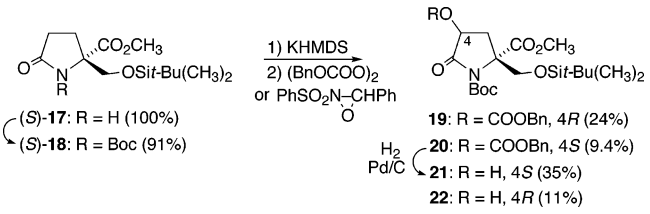
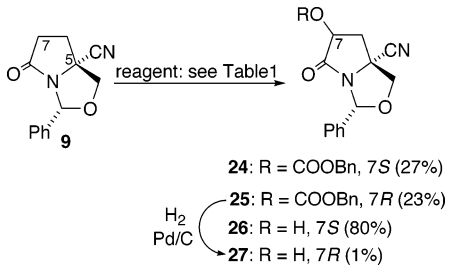
SCHEME 4



SCHEME 5

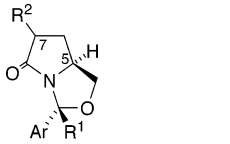


The configuration 4*S* was assigned to **20** after removal of the benzyl carbonate functionality (H_2-10% Pd/C)[19] affording **21**. These disappointing results led us to use the more common reagents oxaziridines.[20] Benzyl *N*-Boc-pyroglutamate has been hydroxylated in 61% yield in this way with complete stereoselectivity,[21] but this yield could not be reproduced in our laboratory,[22] as well as by other groups.[23,24] Nevertheless, the oxidation of **18**−potassium enolate with 2-phenylsulfonyl-3-phenyloxaziridine gave diastereomers **21** and **22** in better yields (47 to 51%) and better, although still modest, diastereoselectivity (dr 3.2:1, Scheme 4). The spectral data, particularly NMR data of **21** and **22**, are very similar and NOESY experiments are not very informative. However, the configuration at C-4 of the major diastereomer **21** was shown to be the same as dysibetaine (4*S*) by a chemical correlation described below (Scheme 6).

Taking accounts of these preliminary results, we turned toward an earlier precursor of dysibetaine involving a bicyclic lactam structure to improve both the efficiency and the diastereoselectivity. Such rigid bicyclic substrates, particularly lactams derived from pyroglutaminol,[25] are known to afford a high degree of diastereoselectivity in several types of reaction.[26−28] Moreover, the intrinsic protection of both nitrogen and primary alcohol in this compound avoided useless steps. The nitrile **9** was chosen for the hydroxylation step (Scheme 5). The behavior of **9** was expected to be closely related to that of models devoid of a cyano substituent at the C-5 center. We postulated that the cyano group may be a minor factor in the diastereofacial selectivity, due to a small effect of this angular substituent on the position of the pyramidal-nitrogen lone pair and on the approach of the electrophile. The analogues **23** have been already hydroxylated by others and by us with 2-phenylsulfonyl-3-phenyloxaziridine (Davis reagent) and MoOPH[29] or MoOPD,[30] and the results are summarized in Table 1 for comparison purposes with our own study (entries 2, 6, 7, 8).

TABLE 1. Hydroxylations at C-7 of Bicyclic Lactams Derived from (*S*)-Pyroglutaminol

entry	lactam	base	reagent	yield (%)	7*S*/7*R*	ref
1	**23a**	KHMDS	Davis reagent	68	1:1	31
2	**23b**	NaHMDS	Davis reagent	83	2:3	this work
3	**23b**	LDA	MoOPD	78	9:1	32
4	**23c**	LDA	MoOPD	53	3:2 or 2:3	33
4	**23d**	LDA	MoOPH	77	100:0	34
6	**9**	KHMDS	$(BnOCOO)_2$	50	∼1:1	this work
7	**9**	KHMDS	Davis reagent	52	3:1	this work
8	**9**	KHMDS	MoOPH	81	80:1	this work



23 a: Ar = p-$CH_3OC_6H_4$, $R^1 = R^2 = H$
23 b: Ar = C_6H_5, $R^1 = R^2 = H$
23 c: Ar = C_6H_5, $R^1 = CH_3$, R^2 = Bn
23 d: Ar = C_6H_5, $R^1 = H$, R^2 = Allyl

Using dibenzyl peroxydicarbonate as electrophile, the diastereomers *endo*-**24** and *exo*-**25** were isolated in 50% yield without stereoselectivity (entry 6), whereas 2-phenylsulfonyl-3-phenyloxaziridine afforded 7-hydroxy derivatives *endo*-**26** and *exo*-**27** in 3:1 dr and 52% yield (entry 7), and this relatively low yield compared with that of the hydroxylation of analogue **23b** (entry 2) remains unclear. The best result was obtained with MoOPH giving rise to *endo*-**26** in 80% yield (entry 8). NOESY experiments are not significant owing to a too small effect between Hβ-6 and H-7 in **27** and also to the absence of hydrogen at C-5. The configurations at C-7 of **26** (7*S*) and **27** (7*R*) were established by ^{1}H NMR and comparison of the observed coupling constants $J_{6,7}$ with the calculated values and those of described analogues[31,32] and were confirmed by subsequent synthesis. The high diastereoselectivity observed with MoOPH favoring the required *endo*-attack could be due to predominant anti-stereoelectronic directing effect of the nitrogen lone pair.[35,36] Chemical correlations between **25**, **27**, and **28** and between **22** and **28**, respectively, ascertained the con-

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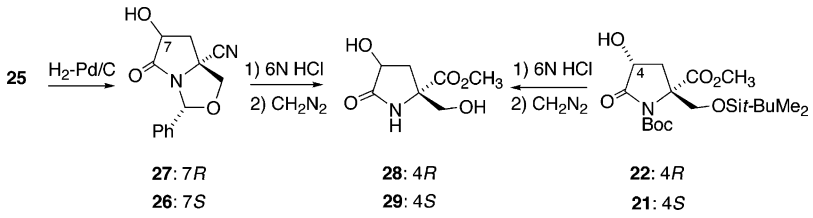
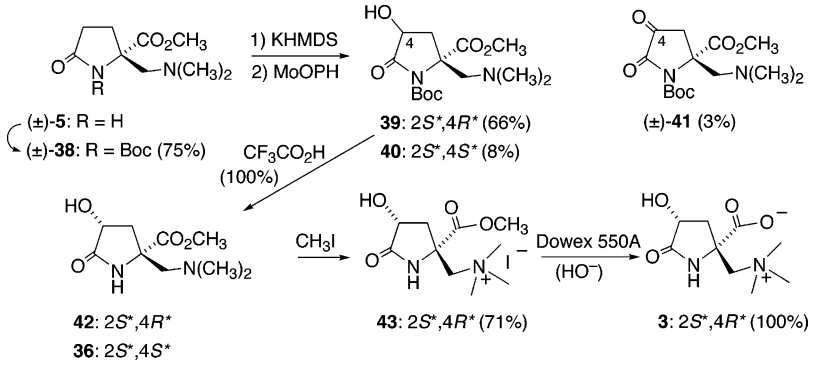
SCHEME 6



SCHEME 7



figurations at the carbon bearing the hydroxyl group (Scheme 6).

Thus, the benzyl carbonate **25** was partially deprotected under hydrogen and 10% Pd/C as catalyst, providing **27** (7*R*). Compound **27** was also correlated with the compound **22** obtained from the monocyclic lactam **18**. So, acidic hydrolysis of **27**, followed by methylation with diazomethane, afforded (2*S*,4*R*)-methyl 4-hydroxy-2-hydroxymethyl pyroglutamate **28** (46% for two steps) also obtained from the compound **22** under the same conditions.

The major 7*S* hydroxy compound **26** was converted to natural dysibetaine **1**, after hydrolysis with 6 N HCl and treatment with excess diazomethane leading to **29** [57% for the two steps, together with some *N*-methylated derivative **30** (6%)]. (2*S*,4*S*)-Methyl 4-hydroxy-2-hydroxymethylpyroglutamate **29** was treated as described for its deoxy analogue deoxydysibetaine **2** (Scheme 3). The monomesylation of the primary alcohol **29** was stopped before completion (starting material recovered 41%) to avoid the reaction of the secondary alcohol at C-4, and the yield of this step (38%) was not optimized. The four last steps were achieved in 56% overall yield.

4-*epi*-Dysibetaine 3. To prepare structural analogues of dysibetaine, we anticipated that the presence of a *N*,*N*-dimethylaminomethyl group at C-2 in monocyclic lactam could direct the hydroxylation at C-4 in a 2,4-*trans* relative configuration. Accordingly, the compound **38** was prepared by classical *N*-Boc protection of (±)-**5** and then deprotonated at C-4 with KHMDS, and the potassium enolate was oxidized with MoOPH[37] to give the 4-hydroxy derivative **39** (66%) together with the diastereomer **40** (8%) and some α-dicarbonylated compound **41 (**ca. 3%, Scheme 7).

The major diastereomer **39** was rapidly converted into its more stable salt trifluoroacetate, whereas prolonged treatment with trifluoroacetic in dichloromethane afforded quantitatively *N*-deprotected compound **42**. In the ^{1}H NMR spectrum of **42**, characteristic chemical shifts and coupling constants are closely related to the data described for the ethyl ester[4a] and agree with a *trans* relationship between the *N*,*N*-methylaminomethyl group at C-2 and the hydroxyl group at C-4. This statement was confirmed by the conversion of **39** into (±)-**4**-*epi*-dysibetaine **3** through the trimethylammonium iodide **43**, as described for its deoxy analogue **2** and shown in the scheme **7**. Obviously, this route constitutes also a formal synthesis of (2*S*,4*R*)-**4**-*epi*-dysibetaine. On the other hand, the conversion of the minor compound **40** into (±)-**36** under the same conditions confirmed its 4*S* configuration.

Conclusion

In conclusion, we took advantage of the access to quaternary stereogenic centers through stereospecific addition of nucleophiles at C-5, starting from silyloxypyrrole **7**, to achieve an efficient and highly diastereoselective synthesis of marine sponge metabolite dysibetaine, as well as deoxy and 4-*epi* analogues. Other applications of this methodology are currently under investigation.

Experimental Section

General Methods. Solvent purification, spectral analyses, and workup procedures were performed as described in the Supporting Information and elsewhere.[38] The chemical shifts

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in ^{1}H NMR (300 MHz) and ^{13}C NMR (75.0 MHz) spectra are given in ppm relative, respectively, to $CHCl_3$ at 7.27 ppm and to the middle line of $CDCl_3$ at 77.14 ppm, or as otherwise indicated.

(±)-2-*N*,*N*-Dimethylaminomethyl-2-methoxycarbonylpyrrolidin-5-one ((±)-5). LiHMDS (1 M in THF, 0.88 mL, 0.88 mmol) was added under argon to a solution of methyl pyroglutamate (60.0 mg, 0.42 mmol) in THF (2.1 mL) cooled at −78 °C. The mixture was stirred for 1.5 h during which time the temperature was allowed to reach −20 to −10 °C, and then it was cooled again to −60 °C before the addition of Eschenmoser's salt (94 mg, 0.5 mmol). The mixture was stirred at −60 °C for 0.5 h and at −60 to −20 °C for 1 h. After addition of saturated solutions of NH_4Cl (1 mL) and $NaHCO_3$ (1 mL) the product was rapidly extracted with CH_2Cl_2. The crude product obtained after usual workup was purified by preparative TLC (eluent: CH_2Cl_2−CH_3OH−NH_4OH 92:8:0.1) affording compound **5** (68.5 mg, 82%) as colorless crystals. Mp: 73 °C. IR: 3220, 2952, 2828, 2778, 1737, 1699, 1456, 1265. MS (ESI, CH_3OH) *m*/*z*: 223 [$(MNa)^+$, 100], 201 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.64 (broad s), 3.75 (s, 3H), 2.86 (d, 1H, J = 13.4 Hz), 2.51 (d, 1H, J = 13.4 Hz), 2.34 (m, 3H), 2.24 (s, 6H), 2.02 (m, 1H). ^{13}C NMR (75.0 MHz, CD_3OD δ = 49.00 ppm) δ: 180.2, 175.2, 68.3, 66.9, 53.0, 47.7, 30.7, 30.3. HRMS (ESI, CH_3OH): calcd for $C_9H_{17}N_2O_3$ $(MH)^+$ 201.1239, found 201.1272.

When some hydrolysis of **5** occurred during the extraction step, the aqueous layer could be acidified with CF_3CO_2H, evaporated to dryness at 30 °C, and treated with CH_2N_2 in Et_2O to recover **5**.

(±)-2-*N*,*N*-Dimethylaminomethyl-5-oxopyrrolidine-2-carboxylic Acid (6). The methyl ester **5** in H_2O was changed into the corresponding carboxylic acid **6**. MS (ESI, H_2O + CH_3CN): 225 $(MK)^+$, 209 $(MNa)^+$, 187 [$(MH)^+$, 100]. ^{1}H NMR (300 MHz, D_2O δ = 4.65 ppm) δ: 3.49 (d, 1H, J = 13.7 Hz), 3.31 (d, 1H, J = 13.7 Hz), 2.78 (s, 6H), 2.34 (m, 2H), 2.20 (m, 1H), 2.04 (m, 1H). ^{13}C NMR (75.0 MHz, D_2O, CD_3OD δ = 49.00 ppm) δ: 182.5, 178.2, 65.3, 64.3, 45.5, 32.4, 29.1. HRMS (ESI, H_2O + CH_3CN): calcd for $C_8H_{14}N_2O_3Na$ $(MNa)^+$ 209.0902, found 209.0935.

(*S*)-2-Hydroxymethylglutamic Acid (10) and (*S*)-Methyl 2-Hydroxymethylpyroglutamate (11). Acidic Hydrolysis of Nitrile 9. To powdered nitrile **9** (767 mg, 3.36 mmol) under argon was added 6 N hydrochloric acid (70.0 mL), and the mixture was stirred at 50 °C until dissolution and then heated at 115 °C for 20 h. After being cooled at rt, the reaction mixture was diluted with water and Et_2O, and each organic layer was washed twice with water. Evaporation of aqueous layers provided crude diacid hydrochloride as pale yellow crystals which were washed with a mixture Et_2O−EtOH 9:1 to give HMG hydrochloride (**10, HCl**, 705.5 mg, 98%).[9,10] **(*S*)-2-Hydroxymethyl-2-methoxycarbonylpyrrolidin-5-one (11).** A solution of diazomethane in ether was added by parts over 2 h to a suspension of this dried diacid hydrochloride (652.0 mg, 3.0 mmol) in methanol (25.0 mL). The mixture was stirred at rt for 18 h and evaporated under reduced pressure. The residue was purified by chromatography (eluent: CH_2Cl_2−MeOH 93:7) to give (*S*)-2-hydroxymethyl-2-methoxycarbonylpyrrolidin-5-one **11** (346 mg, 67%) and *N*-methylated derivative **12** (54 mg, ∼10%) as white crystals. Compound **11**. Mp: 132 °C. $[\alpha]_D$: +37 (*c* 0.45, $CHCl_3$). IR: 3426, 2987, 1736, 1700. MS (ESI, CH_3OH) *m*/*z*: 196 [$(MNa)^+$, 100]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.49 (broad s, 1H), 3.99 (d, 1H, J = 11.6 Hz), 3.79 (s, 3H), 3.65 (d, 1H, J = 11.6 Hz), 2.42 (m, 2H), 2.29 (m, 1H), 2.12 (m, 1H). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ: 178.5, 173.5, 67.8, 67.6, 53.0, 29.9, 27.2. HRMS (ESI, CH_3OH): calcd for $C_7H_{11}NO_4Na$ $(MNa)^+$ 196.0586, found 196.0607.

(*S*)-2-Methanesulfonyloxymethyl-2-methoxycarbonylpyrrolidin-5-one (13). Triethylamine (0.50 mL, 3.59 mmol) was added under argon to a solution of **11** (340.0 mg, 1.96 mmol) in dry CH_2Cl_2, stirred at 0 °C. After 10 min, methanesulfonyl chloride (230 μL, 2.35 mmol) was added, and the mixture was stirred at 0 °C for 2 h. The volatile constituents were evaporated at rt under reduced pressure, and the residue was purified by chromatography (eluent: CH_2Cl_2−CH_3OH 95:5) affording **13** as a colorless oil (422 mg, 86%). $[\alpha]^{24}_D$ = +8.1 (*c* 0.98, $CHCl_3$). IR: 3425, 3024, 3006, 2957, 1747 (sh), 1711, 1367, 1350. MS (ESI, CH_3OH) *m*/*z*: 274 [(MNa^+), 100]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.84 (broad s, 1H), 4.54 (d, 1H, J = 10.0 Hz), 4.24 (d, 1H, J = 10.0 Hz), 3.81 (s, 3H), 3.05 (s, 3H), 2.41 (3 m, 3H), 2.16 (m, 1H). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ: 177.0, 171.5, 72.1, 64.6, 53.6, 37.8, 29.1, 27.7. HRMS (ESI, CH_3OH): calcd for $C_8H_{13}NO_6SNa$ $(MNa)^+$ 274.0361, found 274.0371.

(*S*)-2-Azidomethyl-2-methoxycarbonylpyrrolidin-5-one (14). Sodium azide (520 mg, 8.0 mmol) was added under argon to a solution of **13** (400.0 mg, 1.6 mmol) in DMF (5.0 mL). The mixture was stirred at 65 °C for 72 h. The solvent was evaporated at the same temperature, and the residue was purified by chromatography (eluent: EtOAc) to give **14** (287 mg, 91%) as colorless crystals. Mp: 80 °C. $[\alpha]^{24}_D$ = +34.4 (*c* 1.29, $CHCl_3$). IR: 3426, 3005, 2956, 2928, 2111, 1745 (sh), 1710, 1404, 1334. MS (ESI, CH_3OH) *m*/*z*: 419 $(2MNa)^+$, [221 $(MNa)^+$, 100], 199 $(MH)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.41 (broad s, 1H), 3.86 (d, 1H, J = 12.5 Hz), 3.83 (s, 3H), 3.48 (d, 1H, J = 12.5 Hz), 2.43 (2 m, 2H), 2.35 (m, 1H), 2.10 (m, 1H). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ: 176.9, 172.3, 65.3, 58.0, 53.4, 29.4, 28.7. Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09. Found: C, 42.51; H, 5.16.

(*S*)-2-Aminomethyl-2-methoxycarbonylpyrrolidin-5-one (15), Hydrochloride. To a solution of **14** (150.0 mg, 0.758 mmol) in CH_3OH (3.0 mL), was added 10% Pd/C (20.0 mg), and the mixture was stirred under hydrogen (1 atm) for 18 h at room temperature. The catalyst was filtered off on Celite and washed with CH_3OH. After evaporation to dryness, the residue was disolved in 0.1 N HCl and gave rise to the hydrochloride salt after evaporation (157.9 mg, 100%) as colorless crystals. Mp: 158 °C. $[\alpha]^{23}_D$ = −26.3 (*c* 2.02, CH_3OH). MS (ESI, CH_3OH)) *m*/*z*: 173 $[MH]^+$, 100]. ^{1}H NMR (300 MHz, D_2O δ = 4.65 ppm) δ: 3.72 (s, 3H), 3.37 (d, 1H, J = 15.9 Hz), 3.32 (d, 1H, J = 15.9 Hz), 2.44 (m, 3H), 2.17 (m, 1H). ^{13}C NMR (75.0 MHz, D_2O, CD_3OD δ = 49.00 ppm) δ: 182.5, 173.9, 67.5, 54.8, 44.6, 30.0, 29.2. HRMS (ESI, CH_3OH): calcd for $C_7H_{13}N_2O_3$ $(MH)^+$ 173.0926, found 173.0926.

(*S*)-2-*N*,*N*-Dimethylaminomethyl-2-methoxycarbonylpyrrolidin-5-one ((*S*)-5). Formaldehyde (37% w/v in water, 44 μL) and 10% Pd/C (7.0 mg) were added to a solution of **15, hydrochloride** (63.0 mg, 0.3 mmol) in water (5.0 mL). The mixture was stirrred under hydrogen (45−50 psi) for 24 h. The catalyst was filtered off and washed with CH_3OH, and the solution was evaporated to dryness under vacuum. To the residue in CH_2Cl_2 (5 mL) was added some drops of saturated aqueous solution of $NaHCO_3$, and the mixture was stirred at rt for few minutes and dried over $MgSO_4$. Evaporation to dryness afforded (*S*)-**5** (38.2 mg, 64%) as white crystals. Mp: 77 °C. $[\alpha]^{23}_D$ = +24 (*c* 1.01, $CHCl_3$). HRMS (ESI, CH_3OH): calcd for $C_9H_{17}N_2O_3$ $(MH)^+$ 201.1239, found 201.1256. Spectroscopic data were identical to those of (±)-**5**.

(*S*)-2-Methoxycarbonyl-2-(*N*,*N*,*N*-trimethylammoniummethyl)pyrrolidin-5-one Iodide ((*S*)-16). From (*S*)-2-*N*,*N*-Dimethylamino Derivative (*S*)-5. Iodomethane (0.3 mL), 4.8 mmol) was added to a solution of (*S*)-**5** (32.0 mg, 0.16 mmol) in THF (2.4 mL), and the mixture was stirred for 40 h at rt. The solvent and excess of reagent were evaporated under reduced pressure. The residue was washed several times with CH_2Cl_2 to provide trimethylammonium iodide as white crystals (47 mg, 86%). **From (*S*)-2-Aminomethylated Derivative 15.** Diisopropylethylamine (73 μL, 0.42 mmol) and iodomethane (262 μL, 4.2 mmol) were successively added to a solution of **15** (24.2 mg, 0.14 mmol) in THF (2.1 mL). The mixture was stirred at rt for 40 h. After evaporation to dryness, the white

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solid was washed with CH_2Cl_2. Trimethylammonium iodide (*S*)-**16** was obtained as white crystals (45.0 mg, 94%). $[\alpha]^{24}_D = -12.5$ (*c* 0.77, CH_3OH). MS (ESI, CH_3OH) *m/z*: 215 (M^+, 100). ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.10 (d, 1H, $J = 16$ Hz), 3.80 (s, 3H), 3.77 (d, 1H, $J = 16$ Hz), 3.11 (s, 9H), 2.60−2.32 (3 m, 3H), 2.21 (m, 1H). ^{13}C NMR (75.0 MHz, D_2O, CD_3OD $\delta = 49.00$ ppm) δ: 182.1, 173.6, 70.7, 64.5, 55.7, 55.3, 33.5, 29.3. HRMS (ESI, $H_2O + CH_3CN$): calcd for $C_{10}H_{19}N_2O_3$ $(M)^+$ 215.1396, found 215.1421.

(*S*)-2-Carboxylate-2-(*N,N,N*-trimethylamoniummethyl)-pyrrolidine-5-one (*S*)-2: (*S*)-Deoxydysibetaine (2). Resine Dowex 550A (HO^- form, 327 mg) was added to a solution of (*S*)-**16** (46.7 mg, 0.137 mmol) in dry methanol (2.0 mL). The mixture was stirred at 55 °C for 12 h and cooled, and the resin was filtered off and washed with methanol. Evaporation to dryness gave rise to (*S*)-deoxydysibetaine **2** as white crystals (29.5 mg, 100%).[6]

Under the same conditions, (±)-**2** was prepared from (±)-**16** (85%), which was obtained by *N*-methylation of (±)-**5** (73%).

(5*R*)-5-Cyano-7-hydroxy-2-phenyl-3-oxa-1-aza[3.3.0]-bicyclooctane-8-ones (26) and (27). With 2-Phenylsulfonyl-3-phenyloxaziridine. A solution of KHMDS in toluene (0.5 M, 0.8 mL, 0.4 mmol) was added dropwise under argon to a stirred solution of nitrile **9** (72.5 mg, 0.32 mmol) at −78 °C. The mixture was stirred for 1 h at − 78 °C, and a solution of 2-phenylsulfonyl-3-phenyloxaziridine (101.0 mg, 0.39 mmol) in THF (0.8 mL) was added. The mixture was stirred for 45 min before addition of a saturated aqueous solution of NH_4Cl and was then allowed to warm to rt. After extraction with CH_2Cl_2 and usual workup, the crude product was purified by preparative TLC (eluent: $CH_2Cl_2-CH_3OH$ 93.5:6.5) to give two diastereomers **26** (less polar: 31.2 mg, 40%) and **27** (9.2 mg, 11.9%) as white crystals. **With MoOPH.** A solution of KHMDS in toluene (0.5 M, 18.0 mL, 9.0 mmol) was added dropwise under argon to a stirred solution of nitrile **9** (1.00 g, 4.38 mmol) in anhydrous THF (44.0 mL) at − 78 °C. The mixture was stirred for 10 min at − 78 °C, the cooling bath was removed for 10 min, and the mixture was cooled again at −78 °C before the addition of MoOPH (2.80 g, 6.45 mmol) at once. After being stirred for 2 h at the same temperature, a saturated aqueous solution of NH_4Cl (20 mL) was added, and the mixture was allowed to reach rt and was extracted with EtOAc. After usual workup, the product was purified by chromatography (eluent: $CH_2Cl_2-CH_3OH$ 97:3) affording two diastereomers **26** and **27** (867 mg, 81%) (7*S*: 7*R* = 80:1). **(5*R*,7*S*)-5-Cyano-7-hydroxy-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octan-8-one 26** (856 mg, 80%). Mp: 75 °C. $[\alpha]^{24}_D = +60.3$ (*c* 0.68, $CHCl_3$). IR: 3346, 3022, 2877, 1736. MS (ESI, CH_3OH) *m/z*: 511.0 $(2MNa)^+$, 266.9 $(MNa)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.53 (m, 2H), 7.43 (m, 3H), 6.32 (s, 1H), 4.93 (dd, 1H, $J = 11.1$, 7.9 Hz), 4.56 (d, 1H, $J = 9.3$ Hz), 3.92 (d, 1H, $J = 9.3$ Hz), 3.56 (broad s, 1H), 3.17 (dd, 1H, $J = 13.0$, 7.9 Hz), 2.29 (dd, 1H, $J = 13.0$, 11.1 Hz). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ: 176.4, 135.4, 129.9, 128.9, 126.7, 119.0, 89.6, 76.2, 71.5, 57.6, 40.3. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.43; H, 5.01; N, 11.47. **(5*R*,7*R*)-5-Cyano-7-hydroxy-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octan-8-one 27** (11 mg, 1%). Mp: 159 °C. $[\alpha]^{24}_D = +129.5$ (*c* 0.26, $CHCl_3$). IR: 3774, 2920, 2856, 1715, 1455, 1360, 1343. MS (ESI, CH_3OH) *m/z*: 283 $(MK)^+$, 267 $[(MNa)^+, 100]$, 245 $(MH)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.56 (m, 2H), 7.40 (m, 3H), 6.27 (s, 1H), 4.58 (d, 1H, $J = 9.0$ Hz), 4.53 (dd, 1H, $J = 6.6$, 2.0 Hz), 3.75 (d, 1H, $J = 9.0$ Hz), 2.73 (dd, 1H, $J = 14.5$, 2.0 Hz), 2.53 (dd, 1H, $J = 14.5$, 6.6 Hz). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 176.0, 135.8, 129.9, 129.1, 126.8, 119.5, 89.9, 76.2, 73.9, 60.6, 38.8.

(2*S*,4*S*)-4-Hydroxy-2-hydroxymethyl-2-methoxycarbonylpyrrolidin-5-one (29) from 26. Hydrolysis of 26 with 6 N HCl. HCl (6 N, 80.0 mL) was added under argon to the hydroxylated lactam **26** (750.0 mg, 3.07 mmol), the mixture was stirred at 40 °C until complete dissolution, and the solution was heated at 110 °C for 72 h. After being washed with Et_2O, the aqueous layer was evaporated to dryness to provide the diacide as hydrochloride (728 mg, >100%). A solution of diazomethane in ether was added by parts to a suspension of this diacid (700.0 mg, 2.95 mmol) in methanol (30.0 mL) over 2 h. The mixture was stirred at rt for 18 h and evaporated under reduced pressure. The residue was purified by chromatography (eluent: $CH_2Cl_2-CH_3OH$ 9:1) to give (2*S*,4*S*)-4-hydroxy-2-hydroxymethyl-2-methoxycarbonylpyrrolidin-5-one **29** (328.5 mg, 59%) and *N*-methylated derivative **30** (36.2 mg, 6%) as white solids. **(2*S*,4*S*)-4-Hydroxy-2-hydroxymethyl-2-methoxycarbonylpyrrolidin-5-one 29:** $[\alpha]^{24}_D = -18.3$ (*c* 0.73, CH_3OH). IR: 3299 (broad), 2956, 1701, 1436, 1306. MS (ESI, CH_3OH) *m/z*: 212 $(MNa)^+$. ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.35 (dd, 1H, $J = J' = 8.6$ Hz), 3.83 (d, 1H, $J = 11.7$ Hz), 3.66 (s, 3H), 3.56 (d, 1H, $J = 11.7$ Hz), 2.63 (dd, 1H, $J = 13.5$, 8.6 Hz), 1.84 (dd, 1H, $J = 13.5$, 8.6 Hz). ^{13}C NMR (75.0 MHz, D_2O, CD_3OD $\delta = 49.00$ ppm) δ: 179.6, 175.2, 69.2, 66.6, 65.6, 54.4, 36.5. HRMS (ESI, CH_3OH): calcd for $C_7H_{11}NO_5Na$ $(MNa)^+$ 212.0535, found 212.0540 (100).

(2*S*,4*S*)-4-Hydroxy-2-methoxycarbonyl-2-(methylsulfonylmethyl)pyrrolidin-5-one (31). A solution of mesyl chloride (67 μL, 0.87 mmol) was slowly added to a solution of **29** (151.2 mg, 0.8 mmol) in pyridine (7.5 mL) cooled at 0 °C. The mixture was stirred at the same temperature for 0.5 h before the addition of methanol. After being stirred for additional 0.25 h, the solvents were evaporated under vacuum at rt and the products were separated by preparative TLC (eluent: EtOAc, then $CH_2Cl_2-CH_3OH$ 95:5) to afford (2*S*,4*S*)-4-hydroxy-2-methoxycarbonyl-2-(methylsulfonylmethyl)pyrrolidin-5-one **31** (80 mg, 38%), (2*S*,4*S*)-2-hydroxymethyl-2-methoxycarbonyl-4-methylsulfonyloxypyrrolidin-5-one **32** (17.4 mg, 8%), and dimesylate **33** (14.5 mg, 3%), together with starting diol **29** (61.8 mg, 41%). **(2*S*,4*S*)-4-Hydroxy-2-methoxycarbonyl-2-(methylsulfonylmethyl)pyrrolidin-5-one 31:** $[\alpha]^{24}_D = -20.7$ (*c* 0.41, $CHCl_3$). IR: 3335, 1713, 1436, 1354, 1245, 1174. MS (ESI, CH_3OH) *m/z*: 290 $[(MNa)^+, 100]$. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.97 (broad s, 1H), 4.63 (d, 1H, $J = 10.1$ Hz), 4.42 (dd, 1H, $J = 8.5$, 7.5 Hz), 4.35 (d, 1H, $J = 10.1$ Hz), 3.83 (s, 3H), 3.09 (s, 3H), 2.71 (dd, 1H, $J = 13.8$, 8.5), 2.08 (dd, 1H, $J = 13.8$, 7.5 Hz). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 176.9, 171.0, 71.9, 68.2, 62.3, 53.7, 37.7, 36.3. HRMS (ESI, CH_3OH): calcd for $C_8H_{13}O_7NSNa$ $(MNa)^+$ 290.0310, found 290.0316 (100).

(2*S*,4*S*)-2-Azidomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one (34). Sodium azide (75 mg, 1.15 mmol) was added to a solution of monomesylate **31** (61.0 mg, 0.23 mmol) in DMF (0.6 mL), and the mixture was stirred at rt for 72 h. The solvent was evaporated under vacuum, and the product was purified by preparative TLC (eluent: EtOAc) to give methyl 2-azidomethyl-4-hydroxypyroglutamate **34** (27.0 mg, 70%) as white crystals. Mp = 118 °C. $[\alpha]^{24}_D = +1.0$ (*c* 0.65, CH_3OH). IR: 3277, 2917, 2111, 1738 (sh), 1710, 1436, 1278. MS (ESI, CH_3OH) *m/z*: 237 $[(MNa)^+, 100)]$. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.39 (broad s, 1H), 4.38 (dd, 1H, $J = 8.6$, 7.8 Hz), 3.98 (d, 1H, $J = 12.1$ Hz), 3.84 (s, 3H), 3.53 (d, 1H, $J = 12.1$ Hz), 3.12 (broad, OH), 2.70 (dd, 1H, $J = 13.8$, 7.9 Hz), 2.03 (dd, 1H, $J = 13.8$, 7.7 Hz). ^{13}C NMR (75.0 MHz, D_2O, CD_3OD $\delta = 49.0$ ppm) δ: 179.6, 174.5, 69.1, 66.0, 57.0, 54.6, 37.6. HRMS (ESI, CH_3OH): calcd for $C_7H_{10}N_4O_4Na$ $(MNa)^+$ 237.0600, found 237.0592.

(2*S*,4*S*)-2-Aminomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one (35) and (2*S*,4*S*)-2-*N,N*-Dimethylaminomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one (36). To azide **34** (22.4 mg, 0.105 mmol) in dry CH_3OH (0.9 mL) was added 10% Pd/C (3.5 mg), and the mixture was stirred under hydrogen (1 atm) for 19 h at rt. The catalyst was filtered off on Celite and washed with dry CH_3OH and then dry CH_3OH containing some amounts of NH_3. Evaporation to dryness provided the labile aminomethyl derivative **35** (18.7 mg, 95%). ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.31 dd, 1H, $J = J' = 8.3$ Hz), 3.63 (s, 3H), 2.95 (d, 1H, $J = 13.8$ Hz), 2.83 (d, 1H, $J = 13.8$ Hz), 2.64 (dd, 1H, $J = 13.6$, 8.3 Hz), 1.82 (dd, 1H, $J = 13.6$, 8.3 Hz). ***N*-Dimethylation to 36.**

Formaldehyde (37%w/v in water, 6.0 μL and 10% Pd/C (2.0 mg) were added to a solution of **35, hydrochloride** (10.2 mg, 0.045 mmol) in water (2 mL). The mixture was stirrred under hydrogen (45 psi) for 48 h. The catalyst was filtered off on Celite and washed with H_2O, and the solution was evaporated to dryness under vacuum. To the residue in EtOAc (5 mL) was added dried $NaHCO_3$, and the mixture was stirred at rt for 5 min and filtered. Evaporation to dryness afforded rather unstable **36** (10.0 mg, 100%) which was immediately converted into its trimethylammonium iodide **37**.

(2*S*,4*S*)-4-Hydroxy-2-methoxycarbonyl[(*N*,*N*,*N*-trimethylammonium)methyl]pyrrolidin-5-one Iodide (37). From (2*S*,4*S*)-2-*N*,*N*-Dimethylaminomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one 36. Iodomethane (0.12 mL, 1.93 mmol) was added to a solution of **36** (10.0 mg, 0.046 mmol) in THF (1.2 mL), and the mixture was stirred for 24 h at rt before a second addition of iodomethane (0.04 mL). After being stirred for an additional 24 h, the solvent and excess of reagent were evaporated under reduced pressure. The residue was washed several times with CH_2Cl_2 to provide trimethylammonium iodide **37** as a white solid (13.9 mg, 84%). $[\alpha]^{24}_D = -9.6$ (*c* 0.3, CH_3OH). ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.29 (dd, 1H, $J = 8.3$, 5.8 Hz), 4.05 (d, 1H, $J = 15.0$ Hz), 3.80 (d, 1H, $J = 15.0$ Hz), 2.63 (dd, 1H, $J = 14.4$, 8.3 Hz), 2.06 (dd, 1H, $J = 14.4$, 5.8 Hz). **Directly from (2*S*,4*S*)-2-Aminomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one 35.** Iodomethane (55 μL, 0.88 mmol) was added to a solution of **35** (8.2 mg, 0.044 mmol) in THF (0.66 mL). The mixture was stirred at rt for 16 h before the addition of diisopropylethylamine (14 μL, 0.08 mmol) and iodomethane (27 μL), and the mixture was stirred for an additional 24 h. After evaporation to dryness, the residue was washed 6 times with small amounts of CH_2Cl_2 to give trimethylammonium iodide **37** (comparison of ^1H NMR) as a white solid (9.5 mg, 61%).

Dysibetaine (1). Resine Dowex 550A (HO^- form, 92 mg) was added to a solution of **37** (11.9 mg, 0.33 mmol) in methanol (1.0 mL). The mixture was stirred at 55 °C for 14 h and cooled to rt, and the resine was filtered off and washed with methanol. Evaporation to dryness gave rise to dysibetaine **1** as white solid (7.2 mg, 100%). $[\alpha]^{24}_D = -6.1$ (*c* 0.15, H_2O); [lit.[4a] $[\alpha]_D = -7.1$ (*c* 0.26, H_2O)]. MS (ESI, $H_2O + CH_3CN$) *m*/*z*: 255 $(MK)^+$, 239 $(MNa)^+$, 217 $[(MH)^+$, 100]. ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.25 (dd, 1H, $J = 7.9$, 5.4 Hz), 3.94 (d, 1H, $J = 14.0$ Hz), 3.64 (d, 1H, $J = 14.0$ Hz), 3.11 (s, 9H), 2.59 (dd, 1H, $J = 13.9$, 7.9 Hz), 1.90 (dd, 1H, $J = 13.9$, 5.4 Hz).^{13}C NMR (75.0 MHz, D_2O, CD_3OD $\delta = 49.00$ ppm) δ: 179.6, 176.8, 73.0, 69.0, 64.1, 55.6, 42.3: identical to described data.[4a] HRMS (ESI): calcd for $C_9H_{16}N_2O_4Na$ $(MNa)^+$ 239.1008, found 239.1008.

(±)-1-*tert*-Butoxycarbonyl-2-*N*,*N*-dimethylaminomethyl-2-methoxycarbonylpyrrolidin-5-one (38). To a stirred solution of (±)-**5** (186.2 mg, 0.93 mmol) in CH_3CN (9.3 mL) were successively added under argon DMAP (117.4 mg, 0.96 mmol) and $(Boc)_2O$ (303.8 mg, 1.39 mmol). After the mixture was stirred at rt for 3 h, the solvent was evaporated under reduced pressure at 30 °C. The residue was purified by chromatography (eluent: EtOAc) providing *N*-Boc derivative **38** as a colorless oil (209.5 mg, 75%). IR: 2979, 2953, 2871, 2826, 2775, 1793, 1744, 1716, 1458, 1370, 1315, 1291, 1155. MS (ESI, CH_3CN) *m*/*z*: 323 $(MNa)^+$, 264, 201 (100). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.73 (s, 3H), 3.11 (d, 1H, $J = 14.6$ Hz), 2.90 (d, 1H, $J = 14.6$ Hz), 2.78 (m, 1H), 2.54 (m, 1H), 2.28 (s, 6H), 2.28 (masked m, 1H), 2.01 (m, 1H), 1.49 (m, 9H). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ: 174.8, 173.0, 149.4, 83.7, 69.2, 61.6, 52.4, 48.2, 31.5, 28.0, 27.0. HRMS (ESI, CH_3CN): calcd for $C_{14}H_{24}O_5N_2Na$ $(MNa)^+$ 323.1583, found 323.1554.

(2*S,4*R**)-1-*tert*-Butoxycarbonyl-2-*N*,*N*-dimethylaminomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one (39).** A solution of KHMDS (0.5 M in toluene, 0.85 mL, 0.425 mmol) was added under argon to a stirred solution of dried **38** (57.8 mg, 0.193 mmol) in anhydrous THF (1.90 mL) at −78 °C. The mixture was stirred at −78 °C for 0.5 h and at −30 °C for 10 min, and then it was cooled again at −78 °C before the addition of MoOPH (124.9 mg, 0.288 mmol). After additional stirring at the same temperature for 1.75 h, the mixture was allowed to reach −45 °C for 0.25 h before the addition of aqueous saturated solution of NH_4Cl. The product was extracted with EtOAc and the organic layer was washed rapidly with cooled water. Usual workup and purification by preparative TLC (eluent: EtOAc, then Et_2O) gave rise to rather unstable (2*S**,4*R**)-1-*tert*-butoxycarbonyl-2-*N*,*N*-dimethylaminomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one **39** (66%) together with diastereomer **40** (8%), 3-oxo derivative **41** (3%), and starting product (6%). **39.** IR (film): 3389, 2978, 2929, 2856, 1789, 1745, 1714. MS (ESI, CH_3OH) *m*/*z*: 339 $(MNa)^+$, 239 (100), 217. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.86 (dd, 1H, $J = J' = 7.5$ Hz), 3.74 (s, 3H), 3.09 (d, 1H, $J = 11.2$ Hz), 2.96 (d, 1H, $J = 11.2$ Hz), 2.58 (dd, 1H, $J = 10$, 7.5 Hz), 2.28 (s, 6H), 2.06 (dd, 1H, $J = 10$, 7.5 Hz). ^{13}C NMR (75.0 MHz) δ: 175.1, 171.8, 148.9, 84.3, 68.8, 67.13, 61.4, 52.5, 48.1, 37.8, 28.3. HRMS (ESI, CH_3OH): calcd for $C_{14}H_{24}N_2O_6Na$ $(MNa)^+$ 339.1532, found 339.1530.

(2*S,4*R**)-4-Hydroxy-2-methoxycarbonyl-[*N*,*N*,*N*-trimethylammonium)methyl]pyrrolidin-5-one Iodide (43). (2*S**,4*R**)-2-*N*,*N*-Dimethylaminomethyl-4-hydroxy-2-methoxycarbonylpyrrolidin-5-one 42 (Trifluoroacetate).** A solution of CF_3CO_2H in dry CH_2Cl_2 (10% v/v, 0.162 mL) was added to a solution of **39** (26.1 mg, 0.08 mmol) in dry CH_2Cl_2 and the mixture was stirred at 34 °C for 23 h. Evaporation to dryness at room temperature afforded *N*-deprotected **42** as its trifluoroacetate (27.5 mg, 100%). MS (ESI, H_2O) *m*/*z*: 239 $[(MNa)^+$, 100], 217 $(MH)^+$. ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.40 (dd, 1H, $J \sim J' \sim 8$ Hz), 3.75 (masked d, 1H, $J = 14.5$ Hz), 3.74 (s, 3H), 3.43 (d, 1H, $J = 14.5$ Hz), 2.78 (broad s, 6H), 2.58 (dd, 1H, $J = 14$, 8 Hz), 2.15 (dd, 1H, $J = 14$, 8.8 Hz). HRMS (ESI, H_2O): calcd for $C_9H_{16}N_2O_4Na$ $(MNa)^+$ 239.1008, found 239.1009. ***N*-Methylation to 43.** Diisopropylethylamine (16 μL) and iodomethane (75 μL) were successively added to a solution of trifluoroacetate **42** (12.0 mg, 0.036 mmol) in dry THF (0.6 mL). The mixture was stirred at rt for 46 h, and volatile constituents were evaporated under reduced pressure at rt. The residue was washed several times with small amounts of CH_2Cl_2 and dried to provide trimethylammonium iodide **43** as a white solid (9.2 mg, 71%). ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.48 (dd, 1H, $J = 9.6$, 7.8 Hz), 4.08 (d, 1H, $J = 14.0$ Hz), 3.76 (s, 3H), 3.64 (d, 1H, $J = 14.0$ Hz), 3.05 (s, 9H), 2.60 (dd, 1H, $J = 14.0$, 7.8 Hz), 2.16 (dd, 1H, $J = 14.0$, 9.6 Hz). ^{13}C NMR (75.0 MHz, D_2O) δ: 178.4, 171.9, 69.5, 66.8, 54.5, 54.3, 41.1.

(±)-4-*epi*-Dysibetaine (3). Resine Dowex 550A (HO^- form, 58 mg) was added to a solution of **43** (8.8 mg, 0.025 mmol) in dry methanol (1.0 mL). The mixture was stirred at 55 °C for 24 h and cooled, and the resin was filtered off and washed with methanol. Evaporation to dryness gave rise to racemic 4-*epi*-dysibetaine **3** as a white solid (5.3 mg, 100%). MS (ESI, $H_2O + CH_3CN$) *m*/*z*: 239 $(MNa)^+$, 144 (100). ^1H NMR (300 MHz, D_2O $\delta = 4.65$ ppm) δ: 4.46 (dd, 1H, $J = 10.0$, 7.9 Hz), 3.93 (d, 1H, $J = 14.0$ Hz), 3.48 (d, 1H, $J = 14.0$ Hz), 3.02 (s, 9H), 2.51 (dd, 1H, $J = 13.3$, 7.9 Hz), 1.96 (dd, 1H, $J = 13.3$, 10.0 Hz) identical to described data for (2*S*,4*R*)-4-*epi*-dysibetaine.[4a]

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Supporting Information Available: Experimental procedures for compounds **7**−**9**, **16**, **2**, **17**−**22**, **24**, **25**, and **28**, spectral data of **12**, **17**−**22**, **24**, **25**, **30**, **32**, **33**, **40**, and **41**, and ^1H NMR spectra of compounds **5**−**7**, **11**, **13**, **14**, **16**−**27**, **29**, **31**, **39**, and **42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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