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Total synthesis of (−)-dysibetaine *via* a nitrenium ion cyclization–dienone cleavage strategy†

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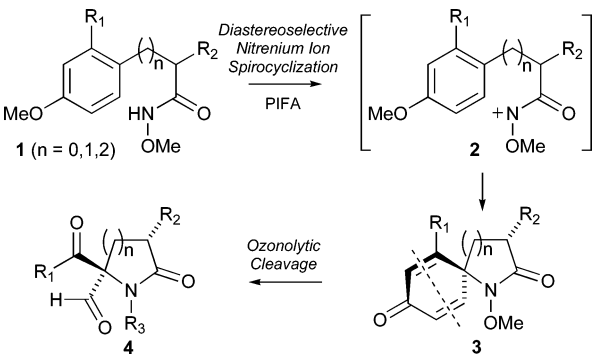
The diastereoselective total synthesis of the marine natural product (−)-dysibetaine is reported. The key steps in this venture are i) a diastereoselective nitrenium ion spirocyclization, which serves to generate the pyrrolidinone ring and quaternary stereocenter of the target, and ii) use of the 2-methoxycyclohexa-2,5-dienone ring formed during cyclization as a masked 2-amino-1,3-dicarbonyl synthon.

Excitatory amino acid (EAA) receptors are widely distributed in the mammalian central nervous system (CNS) and play a role in a range of brain functions and abnormalities, having been implicated in such disorders as epilepsy, Alzheimer's disease, AIDS-related dementia, and Parkinsonism.[1] As a consequence, there is considerable interest in the development of synthetic routes to excitatory amino acids, both natural and otherwise.[2] (−)-Dysibetaine (**5**), an unusual amino acid isolated by Sakai from the marine sponge *Dysidea herbacea*, is a neuroexcitotoxin which may bind to the glutamate receptors present in the CNS of mice.[3] While Sakai unequivocally established the structure of **5** by X-ray crystallography, the absolute stereochemistry of this natural product remained unknown until Snider reported the first total synthesis in 2001.[4,5] Herein, we report the application of a novel nitrenium ion spirocyclization–dienone cleavage strategy to the total synthesis of (−)-dysibetaine.

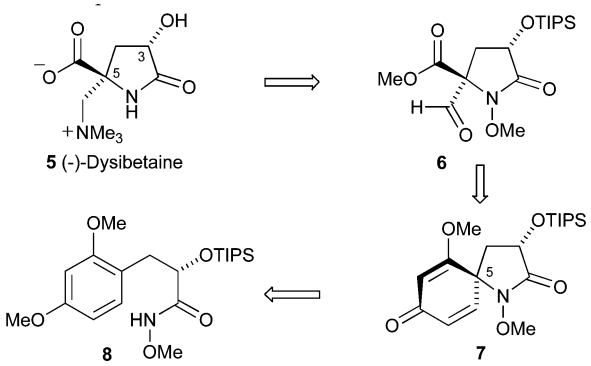
As part of an on-going investigation of the synthetic chemistry of *N*-acylnitrenium ions,[6,7] we recently reported that nitrenium ions **2**, generated through oxidation of α- and β-substituted 3-aryl-*N*-methoxypropionamides **1** with phenyliodine(III) bis(trifluoroacetate) (PIFA), undergo spirocyclization to generate azaspiranes **3** with high levels of 1,2- and 1,3-induction (Scheme 1).[8] Given the ability to control the stereochemistry of the spirocenter in **3**, we were interested in the possibility that oxidative cleavage of the carbon–carbon double bonds of the dienone ring would provide a convenient route to trisubstituted azetidinone, pyrrolidinone and piperidinone derivatives **4**. Significantly, this structural motif is found in a number of biologically-active natural products, including adalinine,[9] lactacystin[10] and dysibetaine (**5**). As outlined in Scheme 2, we anticipated that oxidative spirocyclization of **8** would proceed selectively to generate *anti* dienone **7** as a result of steric strain between the triisopropylsilyl ether and the *o*-methoxyl group on the arene.[11] Having thus established the quaternary stereogenic center and γ-lactam of the target molecule, ozonolytic cleavage of the dienone ring would now reveal β-formyl ester **6**, which would be suitably functionalized to allow introduction of the C-5 (trimethylammonium)methyl group. While substituted cyclohexa-1,4-dienes (obtained through the Birch reduction of arenes) have frequently been employed as latent 1,3-dicarbonyl groups,[12] the use of cyclohexa-2,5-dienones to the same end has not been reported.[13]



Scheme 1 Nitrenium ion spirocyclization–dienone cleavage—a stereoselective route to trisubstituted *N*-heterocycles.

Our route to **5** commenced from α,β-unsaturated ester **9** (Scheme 3). Thus, Sharpless asymmetric dihydroxylation[14] and regioselective reduction of the resulting diol with triethylsilane in the presence of trifluoroacetic acid[15] provided compound **10** in > 98% ee.[16] The hydroxyl group of **10** was protected as the triisopropylsilyl ether and the methyl ester saponified with potassium hydroxide in methanol. The resulting carboxylic acid was treated with isobutyl chloroformate and triethylamine to form the mixed anhydride, which was coupled *in-situ* with methoxylamine to provide compound **8** in excellent overall yield. Following the method previously reported,[6] a solution of **8** in CH_2Cl_2 was added to a suspension of PIFA in MeOH at −78 °C and the mixture allowed to warm to −30 °C over 1 h at which point the reaction was quenched with aqueous sodium bicarbonate. Spirodienone **7** was subsequently isolated as a chromatographically inseparable 9 : 1 mixture of C-5 epimers in near quantitative yield. That the major component of this mixture was the *anti* diastereomer was apparent from the NOESY spectrum, which displayed a cross-peak between the β-hydrogen of the dienone ring at 6.68 ppm and H-4α at 2.03 ppm (Scheme 3).

Ozonolysis of **7** in CH_2Cl_2 at −78 °C followed by reductive workup with dimethyl sulfide generated β-formyl ester **6**, together with a number of other unidentified products. Unfortunately, attempts to purify **6** proved unsuccessful since this compound was unstable and underwent decomposition at room temperature in a matter of hours. Ozonolytic cleavage of **7** in methanol and subsequent reduction with thiourea,[17] on the other hand, proceeded cleanly to provide the methyl hemiacetal of **6**. Since attempts to purify this material by flash chromatography also resulted in



Scheme 2 Synthetic strategy for (−)-dysibetaine.

† Electronic supplementary information (ESI) available: experimental procedures and data including copies of ^{1}H-NMR and ^{13}C-NMR spectra for **5** and all new compounds. See http://www.rsc.org/suppdata/cc/b4/b403081h/

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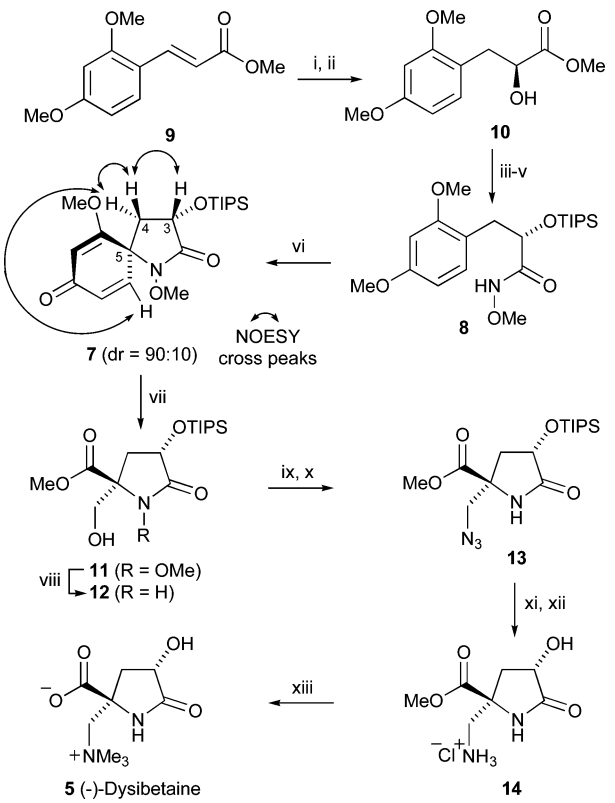
extensive decomposition, we sought to reduce the hemiacetal group *in-situ* in anticipation that primary alcohol **11** would be more tractable. Accordingly, after ozonolysis of **7** in methanol and reduction with thiourea, the reaction mixture was concentrated and immediately treated with sodium triacetoxyborohydride in acetic acid[18] to furnish **11** in excellent overall yield from **3**.

Reductive cleavage of the N–O bond of **11** was accomplished by heating this compound with $Mo(CO)_6$ in aqueous acetonitrile.[19] Exposure of the reaction mixture to air for 24 h prior to isolation served to oxidize the remaining low-valent molybdenum species and facilitated the purification of amide **12**. Introduction of nitrogen functionality at the C-5 hydroxymethyl group of **12** was achieved by exposure of the corresponding mesylate to sodium azide in DMF at elevated temperature, which provided **13** in moderate yield.[20] Attempts to directly install the trimethylammonium group of **5**, by reaction of the mesylate with trimethylamine, were unsuccessful. After removal of the triisopropylsilyl group from **13** using HF in acetonitrile, hydrogenation of the azide group over palladium-on-carbon in the presence of aqueous HCl provided hydrochloride **14**. This compound was now converted to **5** using the three-step protocol reported by Snider for the corresponding ethyl ester.[4] Thus, reductive methylation of **14** by hydrogenation in the presence of formaldehyde provided the corresponding dimethylamine hydrochloride. Since this compound readily underwent ester hydrolysis, it was immediately converted to the natural product through a sequence of quaternization, with methyl iodide and ester hydrolysis using alkaline Dowex 550A resin. In this manner, (−)-dysibetaine (**5**) was obtained in 43% yield, over three steps.[21] A comparison of the spectroscopic and chiroptical properties of this material with that reported by Sakai[3] and Snider[4] indicated a close match.



Scheme 3 *Reagents and conditions*: [i] AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 0 °C, 24 h, 91%; [ii] Et_3SiH, CF_3CO_2H, CH_2Cl_2, 0 °C, 10 min, 84%, > 98% ee; [iii] TIPS-Cl, Im, DMAP, DMF, rt, 36 h, 99%; [iv] KOH, MeOH, reflux, 16 h, 98%; [v] *i*-BuOCOCl, Et_3N; $MeONH_2{\cdot}HCl$, CH_2Cl_2, rt, 16 h, 88%; [vi] PIFA (1.2 equiv.), CH_2Cl_2, MeOH, −78 → −30 °C, 1 h, 99%, dr = 90 : 10; [vii] O_3/O_2, MeOH, −78 °C, 1 h; thiourea, −78 °C → rt, 30 min; $NaBH(OAc)_3$, AcOH, rt, 4 h, 91%; [viii] $Mo(CO)_6$, CH_3CN–H_2O (15 : 1), reflux, 24 h; air, rt, 24 h, 90%; [ix] MsCl, Et_3N, CH_2Cl_2, 0 °C, 3 h, 87%; [x] NaN_3, DMF, 80 °C, 24 h, 63%; [xi] HF, CH_3CN, rt, 4 h, 91%; [xii] H_2 (50 psi), Pd/C (10%), HCl aq., MeOH, rt, 1.5 h, 99%; [xiii] i) H_2 (50 psi), CH_2O, Pd/C (10%), H_2O, rt; ii) MeI, THF, rt, 36 h; iii) Dowex-550A, MeOH, 55 °C, 24 h, 43% (3 steps).

In summary, we report the total synthesis of the marine natural product (−)-dysibetaine (**5**). The central features of this work include i) construction of the 5,5-disubstituted pyrrolidinone ring and C-5 quaternary stereocenter using a diastereoselective acylnitrenium ion spirocyclization and ii) use of the cyclohexa-2,5-dienone ring, generated in this transformation, as a latent 2-amino-1,3-dicarbonyl group. Further application of the nitrenium ion spirocyclization–dienone cleavage strategy disclosed herein is now underway in this laboratory.

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21 Synthetic (−)-dysibetaine (**5**): $[\alpha]^{24}_D$ −8.0 (*c* 0.30, H_2O), [lit.[3] $[\alpha]^{20}_D$ −7.3 (*c* 0.26, H_2O)]; ^{1}H NMR (500 MHz, D_2O) δ 4.20 (dd, *J* = 7.8, 5.4 Hz, 1 H, H-3), 3.89 (d, *J* = 13.9 Hz, 1 H, H-6), 3.59 (d, *J* = 13.9 Hz, 1 H, H-6), 3.05 (s, 9 H, NMe_3), 2.51 (dd, *J* = 14.0, 7.8 Hz, 1 H, H-4), 1.85 (dd, *J* = 14.0, 5.4 Hz, 1 H, H-4); ^{13}C NMR (125 MHz, CD_3OD/D_2O) δ 179.6 (CO), 176.8 (CO), 73.1 (C-3), 69.1 (C-6), 64.1 (C-5), 55.6 (NMe_3), 42.4 (C-4).