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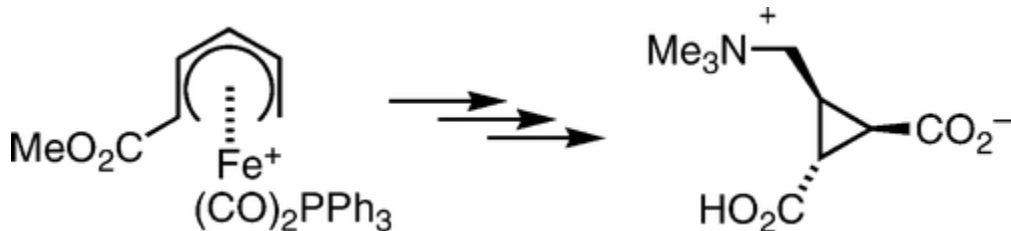
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Abstract



The cyclopropane containing betaine, *rac*-dysibetaine CPa, was prepared from (1-methoxycarbonylpentadienyl)- $\text{Fe}(\text{CO})_2\text{PPh}_3^+$ by nucleophilic addition of nitromethane anion followed by oxidatively induced reductive elimination.

Examination of the common South Pacific sponge *Dysidea herbacea* has led to the isolation of a wide variety of secondary metabolites, including the water-soluble amino acids dysiherbaine (**1**) and neodysiherbaine-A (**2**) which are agonists for mammalian glutamate receptors (Figure 1).^{1,2} Recently, Sakai and co-workers isolated two novel, water-soluble, cyclopropane-containing betaines from *D. herbacea* harvested in Yap State, Micronesia.³ The carbon skeleton and relative stereochemistry of dysibetaine CPa (**3**) and dysibetaine CPb (**4**) were assigned on the basis on their NMR spectral data. Compound **3** displaced kinate from the NMDA-type receptor with IC_{50} of 13 μM . We herein report a synthesis of *rac*-dysibetaine CPa based on organoiron methodology.

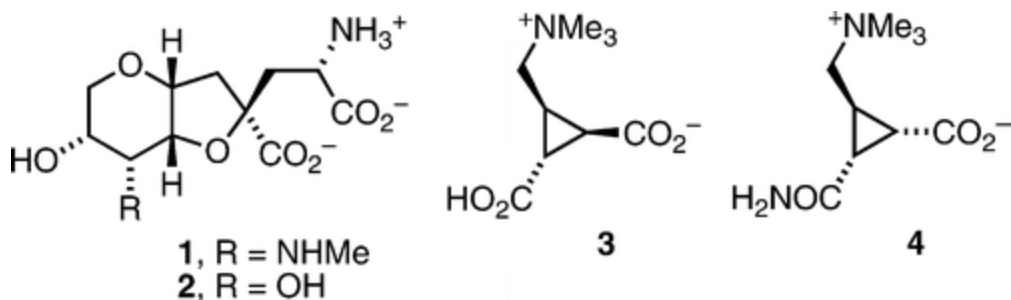
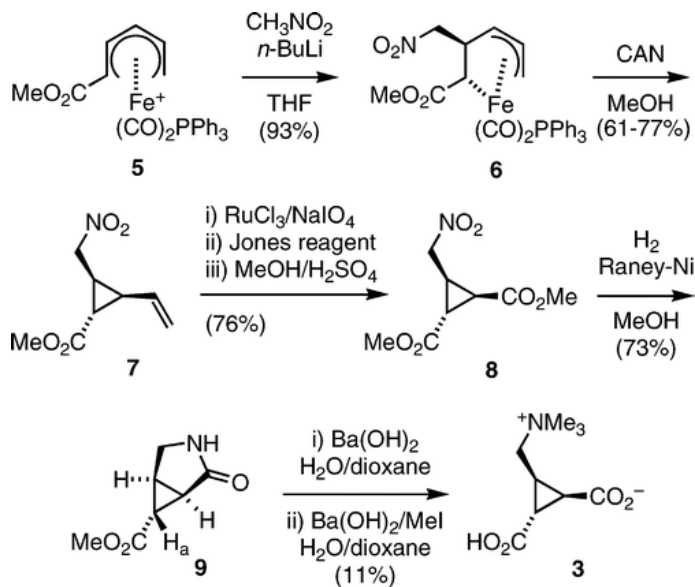


Figure 1 Sponge-derived glutamate agonist aminoacids.

The reaction of (1-methoxycarbonylpentadienyl)iron(1+) cations with certain stabilized nucleophiles or Grignard reagents results in the formation of (2-substituted-3-pentenediyl)iron complexes which upon oxidatively induced–reductive elimination afford stereochemically defined vinylcyclopropane carboxylates.⁴ This methodology was utilized in the synthesis of (carboxycyclopropyl)glycines,^{4a} the C9–C16

alkenylcyclopropane fragment of ambruticin,^{4b} divinylcyclopropanes,^{4c} and bicyclopropanes.^{4c}



Scheme 1

We have previously reported that reaction of (1-methoxycarbonylpentadienyl)iron(1+) cation **5** with the anion generated from nitromethane gave the pentenediyl complex **6** in excellent yield (Scheme 1).⁵ Nucleophilic attack on the face of the pentadienyl ligand opposite to iron is confirmed by the X-ray structure of this complex (Figure 2). Oxidative decomplexation of **6** with ceric ammonium nitrate [CAN] gave the vinylcyclopropanecarboxylate **7**.^{4a} Oxidative cleavage of the vinyl group ($\text{RuCl}_3/\text{NaIO}_4$)⁶ gave a cyclopropylcarboxaldehyde that was further oxidized to the acid with Jones reagent and subjected to Fischer esterification to afford **8**. The appearance of three separate cyclopropane hydrogen signals in the ^1H NMR spectrum of **8** provides evidence for its structural assignment. Reduction of the nitro group with Raney-Ni in methanol proceeded with cyclization to give the lactam **9**. The NMR signal for H_a of **9** (δ 1.83, t, $J = 2.8$ Hz) is consistent with an endo orientation of this proton. Treatment of the lactam with barium hydroxide, followed by exhaustive methylation⁷ of the resultant amine gave (\pm)-**3**. The NMR spectral data for **3** are consistent with those provided in the literature.³

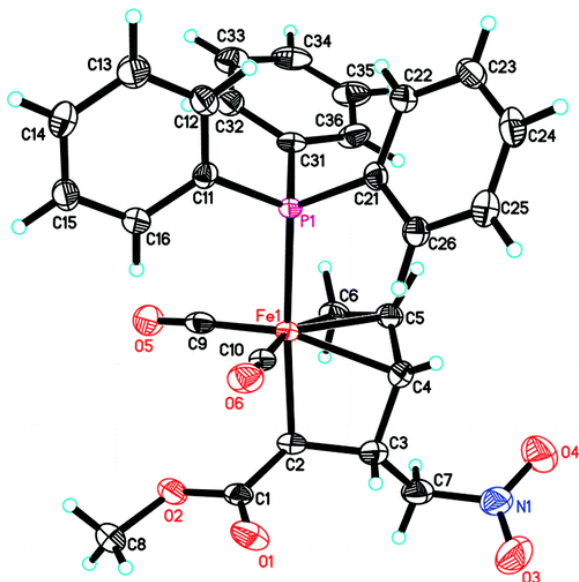


Figure 2 Molecular structure of **6**.

In summary, addition of nitromethane anion to (1-methoxycarbonylpentadienyl)iron(1+) cation **5**, followed by oxidatively induced reductive elimination was used to establish the trisubstituted cyclopropane nucleus of dysibetaine.

Experimental Section[§]

Dimethyl 3-Nitromethylcyclopropane-1,2-dicarboxylate (8).

To a solution of vinylcyclopropane (130 mg, 0.701 mmol) in a mixture of $\text{CCl}_4/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2:2:3 by volume, 7 mL) was added NaIO_4 (615 mg, 2.87 mmol) followed by $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (5.1 mg, 0.019 mmol). The brown reaction mixture became slightly warm and was stirred at room temperature in air for 2 h. The mixture was then diluted with H_2O (15 mL) and CH_2Cl_2 (15 mL). The layers were separated and the black aqueous layer was extracted several times with CH_2Cl_2 . The combined organic layers were dried (MgSO_4) and concentrated to give an aldehyde. To a solution of the aldehyde in reagent grade acetone (5 mL), cooled to 0 °C, was added dropwise Jones reagent (ca. 1.5 mL) until the red-orange color persisted. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with methanol (2 mL) followed by brine (20 mL) and CH_2Cl_2 (20 mL). The

layers were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (MgSO_4) and concentrated to give a gray solid. The solid was taken up in anhydrous methanol (5 mL) and concentrated H_2SO_4 (2 drops) was added. The reaction mixture was heated at reflux under N_2 for 4 h. After this time, the reaction mixture was cooled to room temperature, neutralized with saturated aqueous NaHCO_3 , and extracted several times with ethyl acetate. The combined extracts were dried (MgSO_4) and concentrated. The residue was purified by chromatography (SiO_2 , hexanes–ethyl acetate = 1:1) to afford **8** as a colorless solid (115 mg, 76%). Mp 45–47 °C; ^1H NMR (CDCl_3) δ 2.36 (dd, $J = 4.9, 5.8$ Hz, 1H), 2.38–2.48 (m, 1H), 2.55 (dd, $J = 4.5, 9.0$ Hz, 1H), 3.750 and 3.754 (2 \times s, 6H total), 4.71 (dd, $J = 8.1, 14.7$ Hz, 1H), 4.81 ($J = 6.3, 14.7$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 24.1, 25.9, 26.7, 52.88, 52.93, 71.5, 170.0, 170.3. FAB-HRMS m/z 224.0742 (calcd for $\text{C}_8\text{H}_{11}\text{NO}_6\text{Li}$ (M + Li^+) m/z 224.0746).

6-Methoxycarbonyl-3-azabicyclo[3.1.0]hexan-2-one (**9**).

A solution of **8** (0.19 g, 0.88 mmol) in methanol (17 mL) and a 50% aqueous slurry of Raney-Ni (1 mL) was stirred under H_2 (45 psi) for 4 h. After this time, the mixture was filtered through filter aid and the filter bed was washed with additional methanol. The solvent was evaporated under reduced pressure and the oily aqueous–organic residue was partitioned between CH_2Cl_2 and brine solution. The combined organic extracts were dried (MgSO_4) and concentrated to afford **9** as a colorless powder (0.10 g, 73%). Mp 140–141 °C; ^1H NMR (CDCl_3) δ 1.83 (t, $J = 2.8$ Hz, 1H), 2.36 (br d, $J = 6.9$ Hz, 1H), 2.44–2.51 (m, 1H), 3.45 (d, $J = 11.1$ Hz, 1H), 3.62 (dd, $J = 5.4, 11.1$ Hz, 1), 3.74 (s, 3H), 5.95 (br s, 1H); ^{13}C NMR (CDCl_3) δ 23.8, 25.8, 28.3, 44.1, 52.5, 171.5, 175.5. FAB-HRMS m/z 156.0659 (calcd for $\text{C}_7\text{H}_{10}\text{NO}_3$ (M + H^+) m/z 156.0661).

(±)-Dysibetaine (**3**).

To a solution of $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (0.82 g, 2.60 mmol) in dioxane (4 mL) and water (4 mL) was added **9** (100 mg, 0.65 mmol). The resulting suspension was heated at reflux for 12 h. After gradual

cooling the mixture to 0 °C it was acidified with 25% aqueous H₂SO₄ to precipitate BaSO₄. The white precipitate was removed by filtration through filter aid, and the slightly cloudy solution was made basic with concentrated NH₄OH. The solution was concentrated under vacuum and the resulting milky solution was eluted through Dowex C-211, H⁺ form cation exchange resin, eluting first with water until the eluant did not exhibit any white particles. The column was then eluted with 25% NH₄OH (25 mL), and this latter fraction was lyophilized. The resultant solid was taken up in dioxane (4 mL) and water (4 mL), and Ba(OH)₂·8H₂O (1.6 g, 5.07 mmol) and methyl iodide (0.14 mL, 2.25 mmol) were added. The mixture was heated at 50 °C for 12 h. After the mixture was gradually cooled to 0 °C it was acidified with 25% aqueous H₂SO₄ to precipitate BaSO₄. The white precipitate was removed by filtration through filter aid, and the slightly cloudy solution was made basic with concentrated NH₄OH. The solution was concentrated under vacuum and the resulting milky solution was eluted through Dowex C-211, H⁺ form cation exchange resin, eluting first with water until the eluant did not exhibit any white particles. The column was then eluted with 25% NH₄OH (25 mL), and this latter fraction was lyophilized. The solid was dissolved/suspended in a minimal amount of water, passed through a 0.45 μm filter, and again eluted through Dowex C-211, H⁺ form cation exchange resin, eluting first with water followed by 25% NH₄OH. The NH₄OH fraction was lyophilized to afford (±)-**3** as a colorless amorphous solid (20 mg, 11%). ¹H NMR (600 MHz, D₂O) δ 1.90 (apparent pentet, *J* = 7.8 Hz, 1H), 2.00 (t, *J* = 5.3 Hz, 1H), 2.17 (dd, *J* = 5.3, 9.0 Hz, 1H), 3.17 (s, 9H), 3.65 (dd, *J* = 6.6, 13.8 Hz, 1H), 3.70 (dd, *J* = 7.8, 13.8 Hz, 1H); ¹³C NMR (150 MHz, D₂O) δ 19.7, 29.0, 29.1, 53.1, 64.1, 177.1, 178.9.

Acknowledgment

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Supporting Information Available

Copies of the NMR spectra for **8**, **9**, and *rac*-**3**, and X-ray crystallographic data (in CIF format) for **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1)** (a) Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112–4116. (b) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941–6944. (c) Sakai, R.; Koike, T.; Sasaki, M.; Shimamoto, K.; Oiwa, C.; Yano, A.; Suzuki, K.; Tachibana, K. *Org. Lett.* **2001**, *3*, 1479–1482.
- (2)** For a recent synthesis of dysiherbaine and a compilation of references for dysiherbaine and neodysiherbaine see: Sasaki, M.; Akiyama, N.; Tsubone, K.; Shoji, M.; Oikawa, M.; Sakai, R. *Tetrahedron Lett.* **2007**, *48*, 5697–5700.
- (3)** Sakai, R.; Suzuki, K.; Shimamoto, K.; Kamiya, H. *J. Org. Chem.* **2004**, *69*, 1180–1185.
- (4)** (a) Yun, Y. K.; Godula, K.; Cao, Y.; Donaldson, W. A. *J. Org. Chem.* **2003**, *68*, 901–910. (b) Lukesh, J. M.; Donaldson, W. A. *Chem. Commun.* **2005**, 110–112. (c) Wallock, N. J.; Donaldson, W. A. *Org. Lett.* **2005**, *7*, 2047–2049. (d) Pandey, R. K.; Lindeman, S.; Donaldson, W. A. *Eur. J. Org. Chem.* **2007**, 3829–3831.
- (5)** Barmann, H.; Prahlad, V.; Tao, C.; Yun, Y. K.; Wang, Z.; Donaldson, W. A. *Tetrahedron* **2000**, *56*, 2289–2295.
- (6)** Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
- (7)** Petter, R. C.; Banerjee, S.; England, S. *J. Org. Chem.* **1990**, *55*, 3088–3097. Notably, isolated yields for base hydrolysis/methylation of similar substrates were low (11–38%).
- (8)** Compounds **6** (ref 5) and **7** (ref 4a) were prepared by literature procedures.