

Synthesis of Cyclopropanes via Organoiron  
Methodology: Preparation of *rac*-Dysibetaine  
CPa

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The cyclopropane containing betaine, *rac*-dysibetaine CPa, was prepared from (1-methoxycarbonylpentadienyl)-Fe-(CO)<sub>2</sub>PPh<sub>3</sub><sup>+</sup> 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 dysisibaine (1) and neodysisibaine-A (2) which are agonists for mammalian glutamate receptors (Figure 1).<sup>1,2</sup> Recently, Sakai and co-workers isolated two novel, water-soluble, cyclopropane-containing betaines from *D. herbacea* harvested in Yap State, Micronesia.<sup>3</sup> 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<sub>50</sub> of 13 μM. We herein report a synthesis of *rac*-dysibetaine CPa based on organoiron methodology.

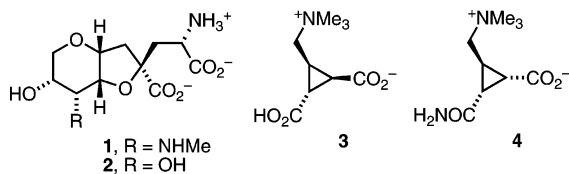


FIGURE 1. Sponge-derived glutamate agonist aminoacids.

The reaction of (1-methoxycarbonylpentadienyl)iron(1+) cations with certain stabilized nucleophiles or Grignard reagents

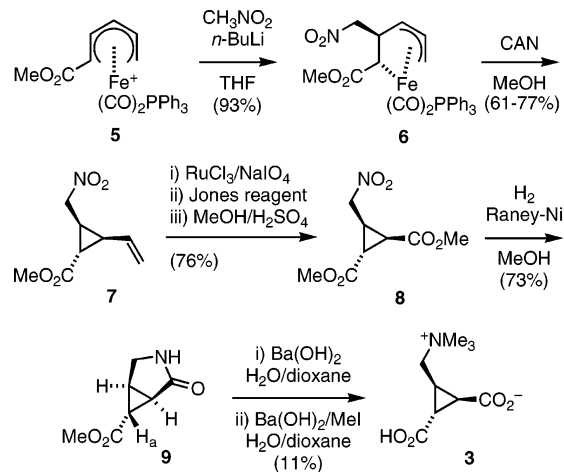
(1) (a) Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112–4116. (b) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941–6944. (c) Sakai, R.; Koike, T.; Sasaki, M.; Shimamoto, K.; Oiwa, C.; Yano, A.; Suzuki, K.; Tachibana, K. *Org. Lett.* **2001**, *3*, 1479–1482.

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results in the formation of (2-substituted-3-pentenediyl)iron complexes which upon oxidatively induced–reductive elimination afford stereochemically defined vinylcyclopropane carboxylates.<sup>4</sup> This methodology was utilized in the synthesis of (carboxycyclopropyl)glycines,<sup>4a</sup> the C9–C16 alkenylcyclopropane fragment of ambruticin,<sup>4b</sup> divinylcyclopropanes,<sup>4c</sup> and bicycyclopropanes.<sup>4c</sup>

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).<sup>5</sup> 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.<sup>4a</sup> Oxidative cleavage of the vinyl group (RuCl<sub>3</sub>/NaIO<sub>4</sub>)<sup>6</sup> 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 <sup>1</sup>H 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 Ha 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 methylation<sup>7</sup> of the resultant amine gave (±)-3. The NMR spectral data for 3 are consistent with those provided in the literature.<sup>3</sup>

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.

(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. *J. Org. Chem.* **2007**, *3829*–3831.

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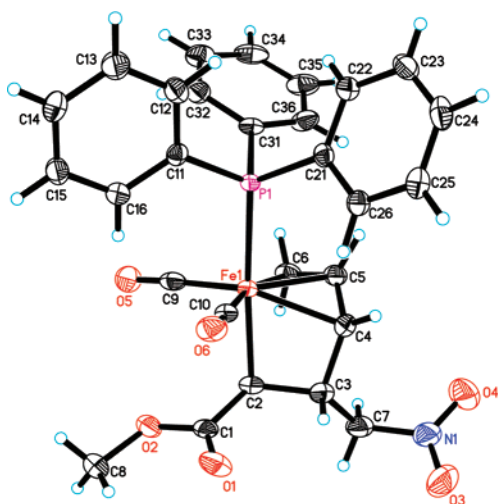


FIGURE 2. Molecular structure of **6**.

### Experimental Section<sup>8</sup>

#### 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  $\text{NaIO}_4$  (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  $\text{H}_2\text{O}$  (15 mL) and  $\text{CH}_2\text{Cl}_2$  (15 mL). The layers were separated and the black aqueous layer was extracted several times with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated to give an aldehyde. To a solution of the aldehyde in reagent grade acetone (5 mL), cooled to  $0^\circ\text{C}$ , 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  $\text{CH}_2\text{Cl}_2$  (20 mL). The layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated to give a gray solid. The solid was taken up in anhydrous methanol (5 mL) and concentrated  $\text{H}_2\text{SO}_4$  (2 drops) was added. The reaction mixture was heated at reflux under  $\text{N}_2$  for 4 h. After this time, the reaction mixture was cooled to room temperature, neutralized with saturated aqueous  $\text{NaHCO}_3$ , and extracted several times with ethyl acetate. The combined extracts were dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by chromatography ( $\text{SiO}_2$ , hexanes–ethyl acetate = 1:1) to afford **8** as a colorless solid (115 mg, 76%). Mp  $45\text{--}47^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  24.1, 25.9, 26.7, 52.88, 52.93, 71.5, 170.0, 170.3. FAB-HRMS  $m/z$  224.0742 (calcd for  $\text{C}_8\text{H}_{11}\text{NO}_6\text{Li}$  ( $\text{M} + \text{Li}^+$ )  $m/z$  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  $\text{H}_2$  (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  $\text{CH}_2\text{Cl}_2$  and brine solution. The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated to afford **9** as a colorless powder (0.10 g, 73%). Mp  $140\text{--}141^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  23.8, 25.8, 28.3, 44.1, 52.5, 171.5, 175.5. FAB-HRMS  $m/z$  156.0659 (calcd for  $\text{C}_7\text{H}_{10}\text{NO}_3$  ( $\text{M} + \text{H}^+$ )  $m/z$  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  $0^\circ\text{C}$  it was acidified with 25% aqueous  $\text{H}_2\text{SO}_4$  to precipitate  $\text{BaSO}_4$ . The white precipitate was removed by filtration through filter aid, and the slightly cloudy solution was made basic with concentrated  $\text{NH}_4\text{OH}$ . The solution was concentrated under vacuum and the resulting milky solution was eluted through Dowex C-211,  $\text{H}^+$  form cation exchange resin, eluting first with water until the eluant did not exhibit any white particles. The column was then eluted with 25%  $\text{NH}_4\text{OH}$  (25 mL), and this latter fraction was lyophilized. The resultant solid was taken up in dioxane (4 mL) and water (4 mL), and  $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$  (1.6 g, 5.07 mmol) and methyl iodide (0.14 mL, 2.25 mmol) were added. The mixture was heated at  $50^\circ\text{C}$  for 12 h. After the mixture was gradually cooled to  $0^\circ\text{C}$  it was acidified with 25% aqueous  $\text{H}_2\text{SO}_4$  to precipitate  $\text{BaSO}_4$ . The white precipitate was removed by filtration through filter aid, and the slightly cloudy solution was made basic with concentrated  $\text{NH}_4\text{OH}$ . The solution was concentrated under vacuum and the resulting milky solution was eluted through Dowex C-211,  $\text{H}^+$  form cation exchange resin, eluting first with water until the eluant did not exhibit any white particles. The column was then eluted with 25%  $\text{NH}_4\text{OH}$  (25 mL), and this latter fraction was lyophilized. The solid was dissolved/suspended in a minimal amount of water, passed through a  $0.45 \mu\text{m}$  filter, and again eluted through Dowex C-211,  $\text{H}^+$  form cation exchange resin, eluting first with water followed by 25%  $\text{NH}_4\text{OH}$ . The  $\text{NH}_4\text{OH}$  fraction was lyophilized to afford (±)-**3** as a colorless amorphous solid (20 mg, 11%).  $^1\text{H NMR}$  (600 MHz,  $\text{D}_2\text{O}$ )  $\delta$  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);  $^{13}\text{C NMR}$  (150 MHz,  $\text{D}_2\text{O}$ )  $\delta$  19.7, 29.0, 29.1, 53.1, 64.1, 177.1, 178.9.

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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>.

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(8) Compounds **6** (ref 5) and **7** (ref 4a) were prepared by literature procedures.