

6-1-2002

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## **Synthesis of cyclopropanes via organoiron methodology: stereoselective preparation of *cis*-2-(2'-carboxycyclopropyl)glycine**

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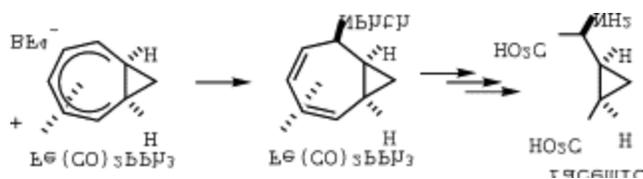
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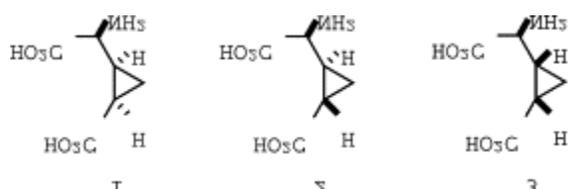
### Abstract

A stereoselective route to *cis*-2-(2'-carboxycyclopropyl)glycine has been developed. *exo*-Nucleophilic addition to the (bicyclo[5.1.0]octadienyl)iron(1+) cation establishes the relative stereochemistry at the cyclopropane ring and the  $\alpha$ -stereocenter. Subsequent removal of the metal and cleavage of the cyclic diene gave the protected target **10**, which upon hydrolysis gave **1**.

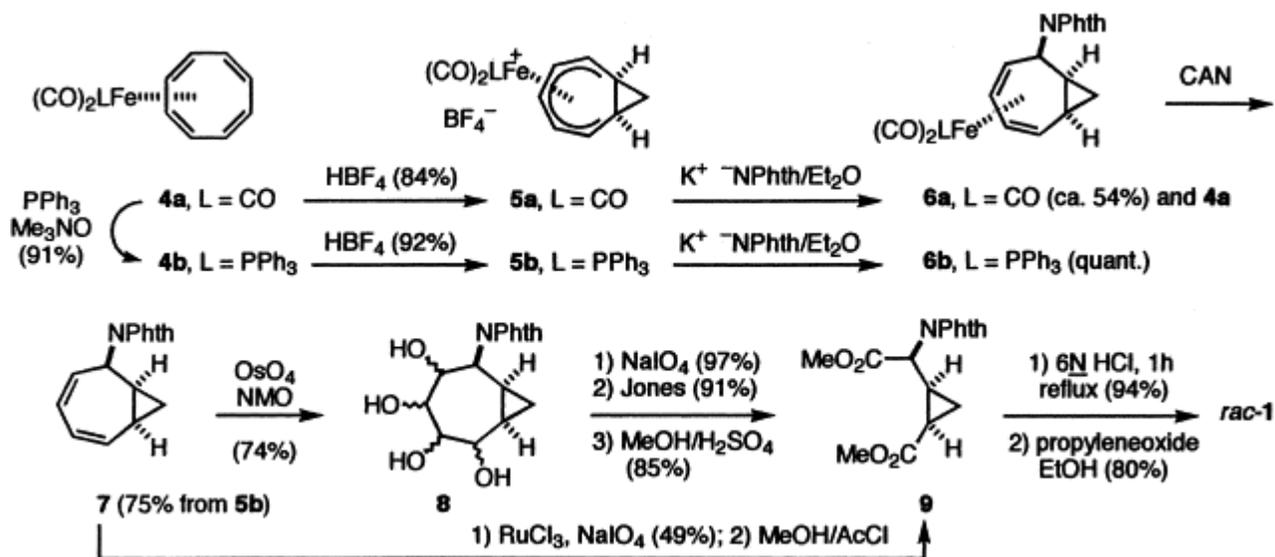
A stereoselective route to *cis*-2-(2'-carboxycyclopropyl)glycine has been developed. *exo*-Nucleophilic addition to the (bicyclo[5.1.0]octadienyl)iron(1+) cation establishes the relative stereochemistry at the cyclopropane ring and the  $\alpha$ -stereocenter.



The *cis*- and *trans*-2-(2'-carboxycyclopropyl)glycines [CCG] (**1** and **2**) were isolated from the seeds of *Aesculus parvifolia* and *Blighia sapida* respectively.<sup>1a</sup> More recently both **1** and **2** as well as **3** were isolated from the stems and seeds of *Ephedra altissima* and *E. foeminea*.<sup>1b</sup> The *cis*-isomer **1** is a potent growth inhibitor of mung bean seedlings.<sup>1a</sup> Since these compounds may be considered conformationally restricted glutamate mimics, they have proven to be 'useful pharmacological tools for analysis of glutamate neurotransmitter systems'.<sup>2</sup> For example, (2*S*,1'*S*,2'*R*)-**1** was found to be a potent and competitive inhibitor of glutamate uptake in glial plasmalemmal vesicles, (2*S*,1'*S*,2'*S*)-**2** is a potent and selective group II mGluRs agonist, while (2*S*,1'*R*,2'*S*)-**3** was found to be a potent and selective NMDA agonist. For this reason, considerable work has been reported on the synthesis of the CCGs and substituted derivatives.<sup>3,4</sup> As part of our overall program on the development of novel iron-mediated methodology for substituted cyclopropane synthesis,<sup>5</sup> we report on the diastereoselective preparation of *cis*-2-(2'-carboxycyclopropyl)glycine (*rac*-**1**).



Protonation of (cyclooctatetraene)Fe(CO)<sub>3</sub> (**4a**) gave the known (bicyclo[5.1.0]octadienyl)Fe(CO)<sub>3</sub><sup>+</sup> cation (**5a**, [Scheme 1](#)).<sup>6</sup> Reaction of **5a** with potassium phthalimide gave a separable mixture of diene complex **6a** and recovered **4a**. In view of the formation of **4a** resulting from deprotonation, it was reasoned that the acidity of the bicyclo[5.1.0]octadienyl ligand could be attenuated by changing the spectator ligand(s). Ligand substitution of one of the carbonyls of **4a** with triphenylphosphine, in the presence of trimethylamine *N*-oxide,<sup>7</sup> gave **4b**. Protonation of **4b** afforded the (dicarbonyl)triphenylphosphine ligated cation **5b**. Reaction of **5b** with potassium phthalimide in ether gave **6b** in quantitative yield.<sup>8</sup> While the crude NMR spectrum of this reaction indicated only the presence of **6b**, chromatography of this crude mixture generated some **4b** (presumably via elimination of phthalimide) at the expense of diminished yields of **6b**. Nucleophilic attack on the *exo*-face of the ligand was tentatively assigned by analogy to the direction of attack of this nucleophile on (cycloheptadienyl)Fe(CO)<sub>3</sub><sup>+</sup> cations.<sup>9</sup> This stereochemical assignment was eventually corroborated by preparation of **1**.



Scheme 1.

Decomplexation of **6b** with CAN gave bicyclo[5.1.0]octa-2,4-diene **7** (75% yield from **5b**, [Scheme 1](#)).<sup>10</sup> The stereochemical assignment of the phthalimide substituent relative to the cyclopropane ring was corroborated by single crystal X-ray diffraction analysis.<sup>11</sup> Catalytic osmylation of **7** afforded a separable mixture of two isomeric tetraols **8a/b**. Glycol cleavage of the mixture **8a/b** with periodate, followed by oxidation with Jones reagent and esterification gave the diester **9** (75%, three steps). Alternatively, oxidation of **7** with  $\text{RuCl}_3/\text{NaIO}_4$  gave the intermediate diacid, albeit in lower overall yield. Brief hydrolysis of **9**, followed by treatment of the resultant hydrochloride salt with propylene oxide gave *rac*-**1**, whose  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data are consistent with the literature values.<sup>4d,f</sup> In summary, the heteroatom and stereochemically rich 2-(2'-carboxycyclopropyl)glycine was prepared in ten steps, 26% yield, from simple achiral (cyclooctatetraene) $\text{Fe}(\text{CO})_3$ . The relative stereochemistry of the three centers is established by *exo*-nucleophilic attack on the (bicyclo[5.1.0]octadienyl) $\text{Fe}(\text{CO})_2\text{PPh}_3^+$  cation **5b**.

## Acknowledgements

Financial support for this work was provided by the National Institutes of Health (GM-42641), the Department of Education (P200A000228) and the Marquette University Integrative Neuroscience Research Center.

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<sup>3</sup>For a review, see: W.A. Donaldson. *Tetrahedron*, 57 (2001), pp. 8589-8627

<sup>4</sup>For previous syntheses of **1**, see: (a) Yamanoi, K.; Ohfuné, Y. *Tetrahedron Lett.* **1988**, 29, 1181–1184;  
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<sup>7</sup>A.J. Pearson, K. Srinivasan. *J. Org. Chem.*, 57 (1992), pp. 3965-3973

<sup>8</sup>A typical experimental procedure follows: To a rapidly stirring suspension of **5b** (4.33 g, 7.65 mmol) in ether (175 mL) under N<sub>2</sub> was added, in portions over a 24 h period, potassium phthalimide (10.11 g, 54.6 mmol). Periodically during this time and for an additional 6 h, the orange ethereal mother liquors were decanted from any solid and the reaction flask charged with additional ether (150 mL). This was repeated until the mother liquors were colorless. The resulting ethereal layers were combined and concentrated to give **6b** (4.81 g) as an orange solid, which was used in the next reaction without further purification. An analytically pure sample could be prepared by chromatography (SiO<sub>2</sub>, hexanes–ethyl acetate gradient=10:1→4:1). Compound **6b**: mp >82°C (decomposed); IR (KBr) 1972, 1913 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.52–0.61 (m, 2H), 1.06 (br pentet, *J*=7.9 Hz, 1H), 1.45–1.56 (m, 1H), 2.28–2.38 (m, 1H), 2.83–2.97 (m, 1H), 4.53–4.64 (m, 1H), 4.90 (br s, 1H), 5.44 (ddd, *J*=0.9, 3.8, 7.6 Hz, 1H), 7.34–7.40 (m, 9H), 7.41–7.50 (m, 6H), 7.66 (m, 2H), 7.78 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 18.10, 18.12, 19.1, 51.4, 57.0 (br), 60.2 (br), 87.0 (br) 92.2 (br), 122.7, 128.5 (d, *J*<sub>CP</sub>=9.2 Hz), 129.8 (d, *J*<sub>CP</sub>=2.0 Hz), 132.8, 133.1, 133.4 (d, *J*<sub>CP</sub>=10.4 Hz), 136.0 (d, *J*<sub>CP</sub>=38.0 Hz), 168.1. Anal. calcd for C<sub>36</sub>H<sub>28</sub>FeNO<sub>4</sub>P: C, 69.13; H, 4.51; N, 2.24. Found: C, 69.28; H, 4.38, N, 2.16.

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<sup>10</sup>A typical experimental procedure follows: To a stirring solution of **6b** (6.35 g, 10.2 mmol) in CH<sub>3</sub>CN (230 mL) was added, in one portion, CAN (5.93 g, 10.6 mmol). After 1 h, TLC monitoring indicated the presence of unreacted **6b**. Additional CAN (2.82 g, 5.07 mmol) was added and the mixture was stirred for an additional 2 h. The reaction mixture was filtered through a small bed of silica gel and the filter bed washed with acetone. The filtrates were concentrated and the resultant orange solid was purified by column chromatography (SiO<sub>2</sub>, hexane–ethyl

acetate=4:1) to give **7** as a colorless solid (1.87 g, 75%). Compound **7**: mp 162–163°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.99 (dddd, *J*=0.9, 4.7, 8.7, 8.7 Hz, 1H), 1.22–1.34 (m, 1H), 1.85–1.95 (m, 1H), 2.25 (ddd, *J*=5.6, 5.6, 5.6 Hz, 1H), 5.43–5.62 (m, 3H), 5.83 (ddd, *J*=2.6, 5.9, 11.5 Hz, 1H), 6.23 (dd, *J*=7.5, 11.6 Hz, 1H), 7.72 (m, 2H), 7.86 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 9.0, 15.2, 43.8, 49.8, 122.6, 123.4, 126.2, 126.9, 132.1, 134.1, 135.2, 167.9. Anal. calcd for C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.20; H, 5.28; N, 5.48.

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