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# Synthesis Of Cyclopropanes *via* Organoiron Methodology: Preparation Of The C9–C16 Alkenylcyclopropane Segment Of Ambruticin<sup>†</sup>

Julie M. Lukesh

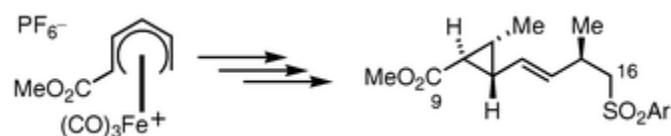
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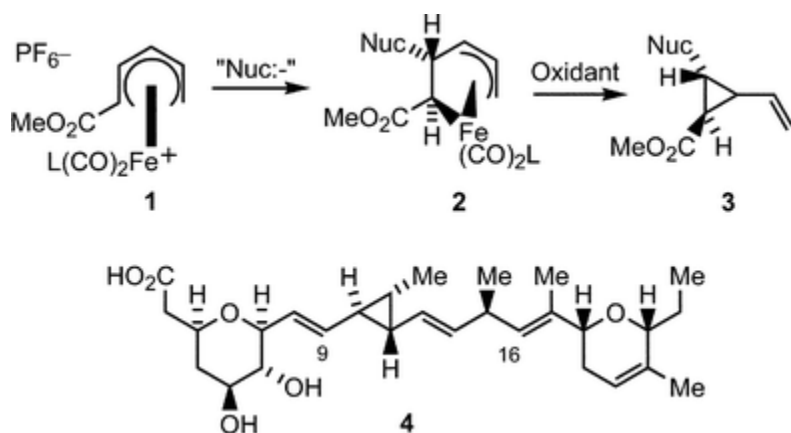
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## Abstract

A synthesis of the C9–C16 segment of ambruticin is described which relies on organoiron methodology to establish the 1,2,3-trisubstituted cyclopropane ring.

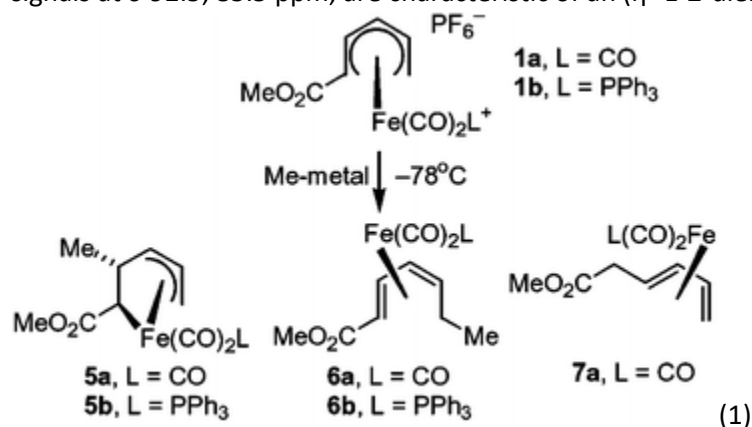


A variety of natural products and pharmaceuticals contain a substituted cyclopropane ring, and numerous synthetic routes to this functionality have been developed.<sup>1</sup> We have recently reported on the scope and mechanism of a novel, iron mediated methodology for the preparation of 1,2,3-trisubstituted cyclopropanes (Scheme 1).<sup>2</sup> This methodology relies on nucleophilic addition of stabilized carbon nucleophiles to (1-methoxycarbonylpentadienyl)iron cation **1** to generate (pentenediyl)iron complexes **2**. The oxidative induced-reductive elimination of complexes **2** affords vinylcyclopropane carboxylates **3**. Herein we report on the reaction of cations **1** with methyl nucleophiles and the subsequent oxidative decomplexation. The resultant cyclopropane product was utilized in synthesis of the C9–C16 alkenylcyclopropane segment of ambruticin **4**, an orally active antifungal agent isolated from *Polyangium cellulorum* var. *fulvum*.<sup>3</sup>



**Scheme 1** Synthesis of vinylcyclopropanes *via* organoiron methodology.

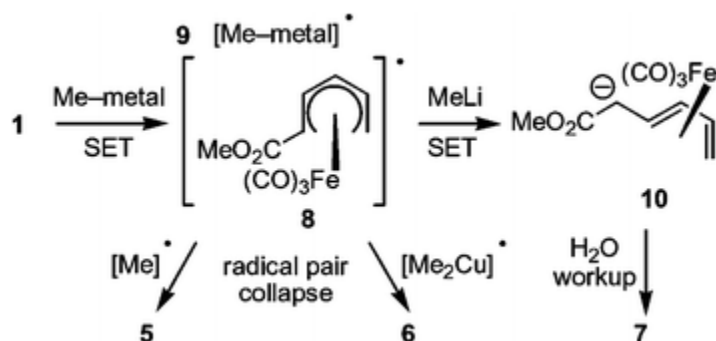
Reaction of the tricarbonyl ligated cation **1a** with dimethylcuprate gave diene complex **6a** along with a minor amount of (pentenediyl)iron complex **5a** (Table 1). In contrast, reaction of **1a** with  $\text{CH}_3\text{Li}$  in  $\text{CH}_2\text{Cl}_2$  gave predominantly the (pentenediyl)iron complex **5a** along with variable amounts of the known<sup>4</sup> (methyl 3,5-hexadienoate) $\text{Fe}(\text{CO})_3$  (**7a**), while reaction of the dicarbonyl(triphenylphosphine) ligated cation **1b** with  $\text{MeLi}/\text{CH}_2\text{Cl}_2$  gave the pentenediyl complex **5b**. The structures of pentenediyl complexes **5a/b** and diene complex **6a** were assigned on the basis of their NMR spectral data. In particular, for the pentenediyl complexes **5a/b**, the methyl resonance for each ( $\delta$  0.70 and 0.61 ppm respectively) appears as a doublet, indicative of only a single adjacent non-equivalent proton. Additionally, a  $^{13}\text{C}$  NMR signal at *ca.*  $\delta$  13–15 ppm and a  $^1\text{H}$  NMR signal at *ca.*  $\delta$  0.0 (d) ppm are characteristic of a carbon  $\sigma$ -bonded to iron and its attached proton.<sup>5</sup> For the diene complexes **6a**, the signal for the methylprotons ( $\delta$  0.96 ppm) appears as a triplet, indicative of two adjacent non-equivalent protons. Additionally, two  $^1\text{H}$  NMR at  $\delta$  6.05 (dd) and 5.26 (dd) ppm and two  $^{13}\text{C}$  NMR signals at  $\delta$  92.5, 85.5 ppm, are characteristic of an ( $\eta^4$ -*E-Z*-dienoate)iron complex.<sup>5</sup>



**Table 1** Reaction of (1-methoxycarbonylpentadienyl)iron(1+) cations with methyl nucleophiles

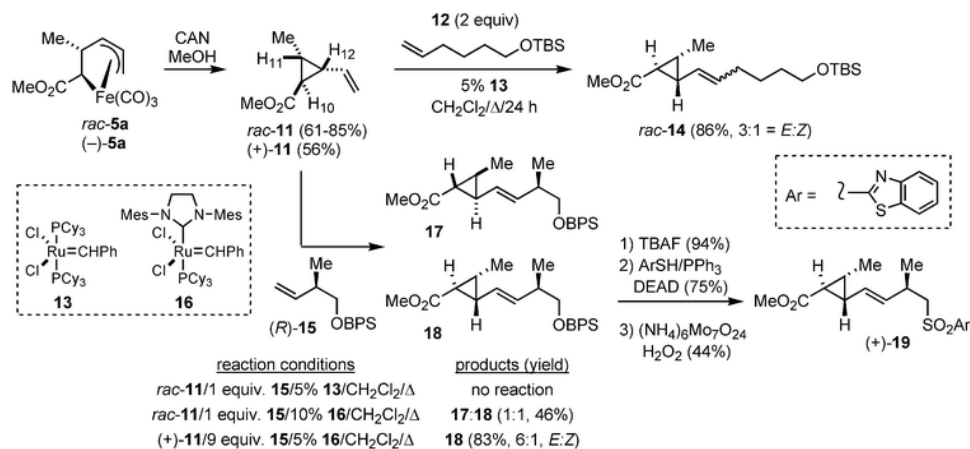
Cation	Conditions	Products (isolated yields, %)
<i>rac</i> - <b>1a</b>	MeLi/CuBr/THF/Et <sub>2</sub> O	<b>5a</b> + <i>E,Z</i> - <b>6a</b> (1 : 14, 58%)
<i>rac</i> - <b>1a</b>	MeLi/CH <sub>2</sub> Cl <sub>2</sub>	<b>5a</b> (46–71%), <b>7a</b> (0–25%)
(1 <i>S</i> )- <b>1a</b>	MeLi/CH <sub>2</sub> Cl <sub>2</sub>	(-)- <b>5a</b> (49%), <b>7a</b> (4%)
<i>rac</i> - <b>1b</b>	MeLi/CH <sub>2</sub> Cl <sub>2</sub>	<b>5b</b> (56–66%)

Formation of the products is rationalized by initial single electron-transfer from either methylcuprate or methyl lithium to afford a (pentadienyl)iron radical **8** and methyl–metal radical **9** (Scheme 2). Kochi has previously reported that certain nucleophilic additions to (pentadienyl)iron cations proceed *via* initial electron-transfer.<sup>6</sup> In the case of methylcuprate collapse of the radical pair occurs *via* C–C bond formation at the terminal carbon, while for methyl lithium collapse of the radical pair occurs *via* C–C bond formation at the internal C2 carbon. If the radical pair **8** : **9** escapes the solvent cage, then a second single electron transfer to **8** generates the pentadienyl anion **10**. Aqueous work-up of the reaction mixture gives the protonated product **7**. Notably, we have previously demonstrated the generation and alkylation of the (pentadienyl)iron anion **10** by deprotonation of **7**.<sup>4</sup>



**Scheme 2** Mechanism for addition of methyl nucleophiles.

Oxidatively induced-reductive elimination of **5a** with excess ceric ammonium nitrate (CAN) cleanly gave the vinylcyclopropane **11** (Scheme 3). The relative stereochemistry of **11** was assigned on the basis of its <sup>1</sup>H NMR coupling data. The large coupling (*ca.* 9.6 Hz) between H11 and H12 (ambruticin numbering) indicates a *cis* relationship while smaller couplings between H10 and H11 and between H10 and H12 (*ca.* 4.9 Hz each) indicate a *trans* relationship.<sup>7</sup> Preparation of optically active (+)-**11** was accomplished in a similar fashion from the optically active cation (1*S*)-**2**.<sup>8</sup>



**Scheme 3** Oxidatively induced-reductive elimination and olefin cross-metathesis.

Introduction of the C13–C14 linkage by olefin cross-metathesis<sup>8,10</sup> was envisioned. Reaction of *rac*-**11** with **12** (2 equiv.) in the presence of (PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>Ru=CHPh (**13**, 10 mol%) gave alkenylcyclopropane **14** (86%) as a mixture of *E*- and *Z*-isomers (Scheme 3). The isolation of greater than a statistical yield of the cross-metathesis product indicates that the vinylcyclopropane **11** may be considered a “type-II” olefin in terms of its reactivity.<sup>9</sup> In comparison, reaction of *rac*-**11** with (*R*)-**15** (1 equiv.)<sup>11</sup> in the presence of **13** (5 mol%) gave no metathesis product after 24 h at reflux. Use of the more active IMe(PCy<sub>3</sub>)Cl<sub>2</sub>Ru=CHPh (**16**, 10 mol%) gave an inseparable mixture of diastereomeric alkenylcyclopropanes **17** and **18** (46%), along with homodimers resulting from self-metathesis (*ca.* 45% combined yield of homodimers). This statistical ratio of products indicates that **11** and **15** have comparable rates of cross-metathesis and homodimerization. With these results in hand, cross-metathesis of (+)-**11** with a nine-fold excess of (*R*)-**15** gave only **18** as a mixture of *E*- and *Z*-isomers (6 : 1 ratio, 83% yield). Transformation of **18** into the sulfone **19** was accomplished by cleavage of the silyl ether, Mitsunobu reaction of the primary alcohol with 2-mercaptobenzothiazole, and finally oxidation with ammonium molybdate tetrahydrate.

In summary, a short route to the C9–C16 alkenylcyclopropane segment (**19**) of the structurally complex antifungal agent ambruticin was developed based on organoiron methodology.

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## Footnote

1. † This manuscript is dedicated to Prof. Michael A. McKinney on the occasion of his 65th birthday.