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Synthesis Of Cyclopropanes*via* Organoiron Methodology: Preparation Of The C9–C16 Alkenylcyclopropane Segment Of Ambruticin†

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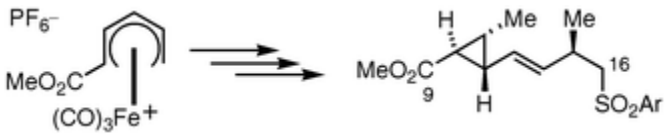
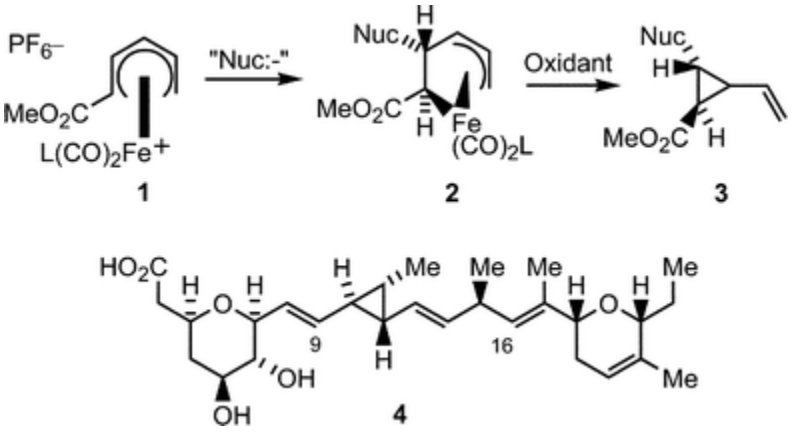
Abstract

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.

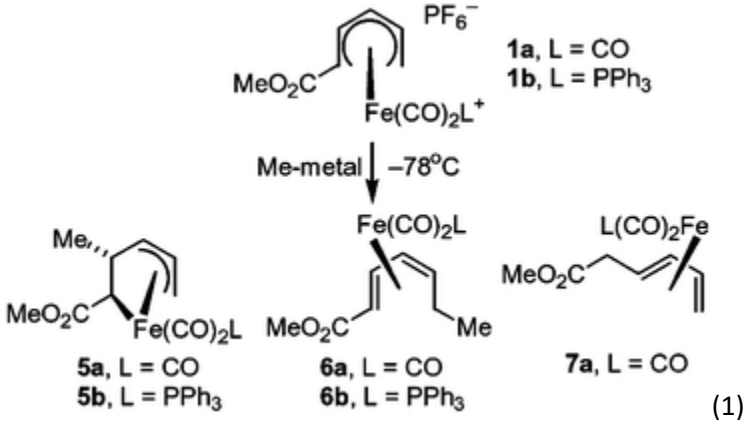


A variety of natural products and pharmaceuticals contain a substituted cyclopropane ring, and numerous synthetic routes to this functionality have been developed.[1] We have recently reported on the scope and mechanism of a novel, iron mediated methodology for the preparation of 1,2,3-trisubstituted cyclopropanes (Scheme 1).[2] 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 cellulosum var. fulvum*.[3]



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 CH_3Li in CH_2Cl_2 gave predominantly the (pentenediyl)iron complex **5a** along with variable amounts of the known[4] (methyl 3,5-hexadienoate)$Fe(CO)_3$ (**7a**), while reaction of the dicarbonyl(triphenylphosphine) ligated cation**1b** with $MeLi/CH_2Cl_2$ 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 (δ 0.70 and 0.61 ppm respectively) appears as a doublet, indicative of only a single adjacent non-equivalent proton. Additionally, a ^{13}C NMR signal at *ca.*δ 13–15 ppm and a ^1H NMR signal at *ca.*δ 0.0 (d) ppm are characteristic of a carbon σ-bonded to iron and its attached proton.[5] For the diene complexes **6a**, the signal for the methylprotons (δ 0.96 ppm) appears as a triplet, indicative of two adjacent non-equivalent protons. Additionally, two ^1H NMR at δ 6.05 (dd) and 5.26 (dd) ppm and two ^{13}C NMR signals at δ 92.5, 85.5 ppm, are characteristic of an (η^4-*E*-*Z*-dienoate)iron complex.[5]

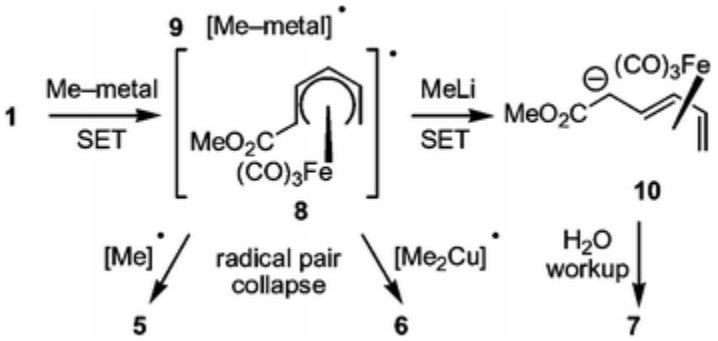


(1)

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

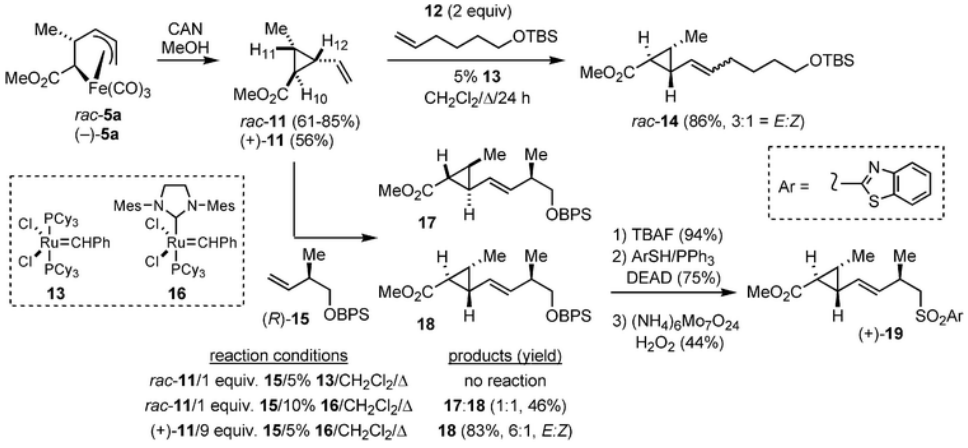
Cation	Conditions	Products (isolated yields, %)
rac-**1a**	MeLi/CuBr/THF/Et_2O	**5a** + *E,Z*-**6a** (1 : 14, 58%)
rac-**1a**	MeLi/CH_2Cl_2	**5a** (46–71%), **7a** (0–25%)
(1*S*)-**1a**	MeLi/CH_2Cl_2	(–)-**5a** (49%), **7a** (4%)
rac-**1b**	MeLi/CH_2Cl_2	**5b** (56–66%)

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.[6] 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**.[4]



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 ^{1}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.[7] Preparation of optically active (+)-**11** was accomplished in a similar fashion from the optically active cation (1*S*)-**2**.[8]



Scheme 3 Oxidatively induced-reductive elimination and olefincross-metathesis.

Introduction of the C13–C14 linkage by olefincross-metathesis[8,10] was envisioned. Reaction of *rac*-**11** with **12** (2 equiv.) in the presence of $(PCy_3)_2Cl_2Ru{=}CHPh$ (**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.[9] In comparison, reaction of *rac*-**11** with (*R*)-**15** (1 equiv.)[11] in the presence of **13** (5 mol%) gave no metathesis product after 24 h at reflux. Use of the more active $IMes(PCy_3)Cl_2Ru{=}CHPh$ (**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.