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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\(^1\)a 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\(_3\)Li in CH\(_2\)Cl\(_2\) 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\(_2\)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 \(^1^3\)C NMR signal at ca.\(\delta\) 13–15 ppm and a \(^1\)H NMR signal at ca.\(\delta\) 0.0 (d) ppm are characteristic of a carbon \(\sigma\)-bonded to iron and its attached proton.\(^5\) 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 \(^1\)H NMR at \(\delta\) 6.05 (dd) and 5.26 (dd) ppm and two \(^1^3\)C NMR signals at \(\delta\) 92.5, 85.5 ppm, are characteristic of an (\(\eta^4\)-E-Z-dienoate)iron complex.\(^5\)

**Table 1** Reaction of (1-methoxycarbonylpentadienyl)iron(1+) cations with methyl nucleophiles
<table>
<thead>
<tr>
<th>Cation</th>
<th>Conditions</th>
<th>Products (isolated yields, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rac-1a</td>
<td>MeLi/CuBr/THF/Et₂O</td>
<td>5a + E,Z-6a (1 : 14, 58%)</td>
</tr>
<tr>
<td>rac-1a</td>
<td>MeLi/CH₂Cl₂</td>
<td>5a (46–71%), 7a (0–25%)</td>
</tr>
<tr>
<td>(1S)-1a</td>
<td>MeLi/CH₂Cl₂</td>
<td>(−)-5a (49%), 7a (4%)</td>
</tr>
<tr>
<td>rac-1b</td>
<td>MeLi/CH₂Cl₂</td>
<td>5b (56–66%)</td>
</tr>
</tbody>
</table>

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. 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.

![Scheme 2](image)

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 ¹H NMR coupling data. The large coupling (ca. 9.6 Hz) between H11 and H12 (ambutricin 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. Preparation of optically active (+)-11 was accomplished in a similar fashion from the optically active cation (1S)-2.

![Scheme 3](image)

Scheme 3 Oxidatively induced-reductive elimination and olefin cross-metathesis.
Introduction of the C13–C14 linkage by olefin cross-metathesis\textsuperscript{8,10} was envisioned. Reaction of \textit{rac}-11 with 12 (2 equiv.) in the presence of (PCy$_3$)$_2$Cl$_2$Ru=CHPh (13, 10 mol\%) gave alkenylcyclopropane 14 (86\%) as a mixture of \textit{E}- and \textit{Z}-isomers (Scheme 3). The isolation of greater than a statistical yield of the cross-metathesis product indicates that the vinylcyclopropane11 may be considered a “type-II” olefin in terms of its reactivity.\textsuperscript{9} In comparison, reaction of \textit{rac}-11 with (\textit{R})-15 (1 equiv.)\textsuperscript{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$_2$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 (\textit{R})-15 gave only 18 as a mixture of \textit{E}- and \textit{Z}-isomers (6 : 1 ratio, 83\% yield). Transformation of 18 into the sulfone19 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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Notes and references


8. (1S)-1a was prepared from (+)-tricarbonyl(methyl 6-oxo-2,4-hexadienoate)iron. C. Tao and W. A.


10. For other examples of olefin cross-metathesis of vinylcyclopropanes see: C. Verbicky and C. K.
2000, 2, 1431.


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