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Synthesis of Cyclopropanes via Organoiron Methodology: Stereoselective Preparation of Bi(cyclopropyl)s

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Cyclopropanation of [2-(alkenyl)pentenediyl]$Fe(CO)_3$ complexes (**4**) proceeds in a diastereoselective fashion to afford [2-(cyclopropyl)pentenediyl]$Fe(CO)_3$. The relative stereochemistry of the products was established by X-ray crystallography. The diastereoselectivity is rationalized on approach of the cyclopropanation reagent on the sterically more exposed face of **4**. Oxidatively induced reductive elimination afforded stereodefined bi(cyclopropyl)s.

Introduction

There has been a great deal of interest[1] in the synthesis of poly(cyclopropyl) frameworks, in particular since these appear in the antifungal agent FR-900848 (**1**)[2] and in U-106305 (**2**),[3] which possesses potent inhibitory activity against the cholesteryl ester transfer protein (Figure 1).

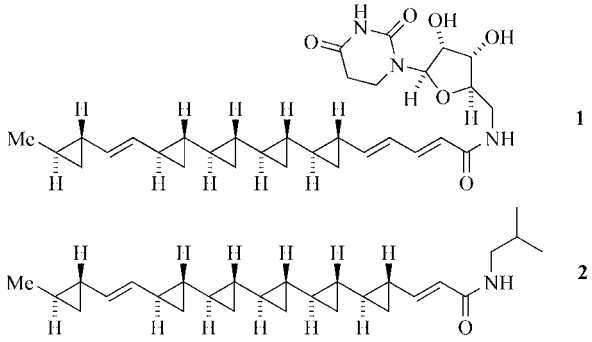
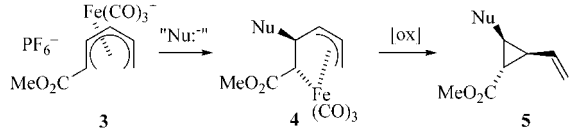


Figure 1. Poly(cyclopropyl) natural products.

The reaction of the [1-(methoxycarbonyl)pentadienyl]-iron(1+) salt **3** with certain nucleophiles (e.g. malonates, methyllithium) results in the formation of (2-substituted 3-pentene-1,5-diyl)iron complexes **4** (Scheme 1). Oxidatively induced reductive elimination of complexes **4** affords stereochemically defined vinylcyclopropanecarboxylates **5**.[4] We have utilized this reactivity for the synthesis of (carboxycyclopropyl)glycines[4a] and the C9–C16 alkenylcyclopropane fragment of ambruticin.[4b] More recently, we have found that the reaction of **3** with alkenyl Grignard reagents gives (2-alkenylpentenediyl)iron complexes.[5] The planar chirality of transition-metal complexes, including tricarbonyl(diene)iron complexes, has been utilized for diastereoselective cyclopropanation reactions.[6] We herein report on the reactivity of (2-alkenylpentadienyl)iron complexes towards cyclopropanation and the further elaboration of the products into bi(cyclopropyl)s.[7]



Scheme 1. Organoiron methodology for the synthesis of vinylcyclopropanecarboxylates.

Results and Discussion

The attempted reaction of (2-vinylpentenediyl)iron complex **4a** with methyl diazoacetate in the presence of either $Rh_2(OAc)_4$ or $Cu(OTf)_2$ gave only recovered **4a** and a mixture of dimethyl fumarate/dimethyl maleate. In contrast, reaction of **4a** in $CHCl_3$ with 50% aqueous NaOH and cetyltrimethylammonium bromide[8] (80 h) proceeded to 83% completion to afford a separable mixture of diastereomeric complexes **6** and **7** (2:1) along with unreacted starting material **4a** (Scheme 2). The major product **6** was separable from **7**/**4a** by column chromatography; pure **7** could be separated from **4a** by recrystallization. The relative configuration of **7** was elucidated by X-ray diffraction analysis (Figure 2).[9]

Cross-metathesis of **4a** with (2*Z*)-1,4-diacetoxy-2-butene (3 equiv.) was successfully accomplished using Grubbs' 2nd generation catalyst (Scheme 2).[10] Hydrolysis of the allylic acetate **4b** afforded the allylic alcohol **4c**. Subjecting **4c** to Simmons–Smith conditions gave a separable mixture of dia-

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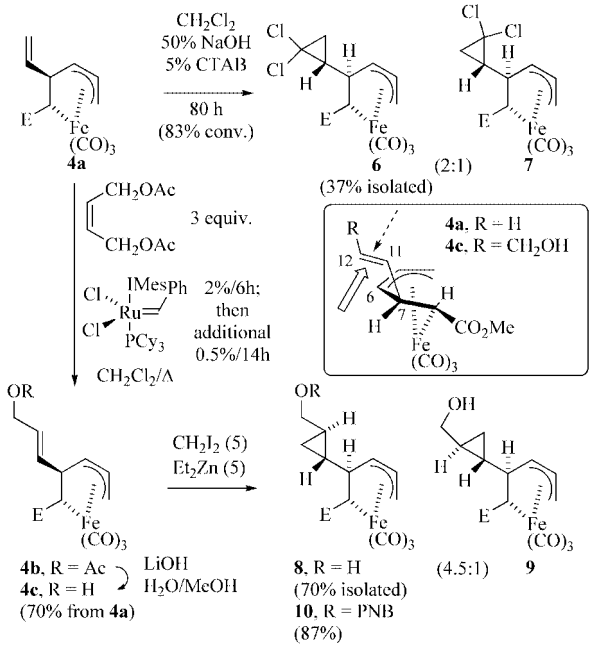
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 2. Cyclopropanation of (2-alkenylpentenediyl)Fe(CO)$_3$ (E = CO_2Me).

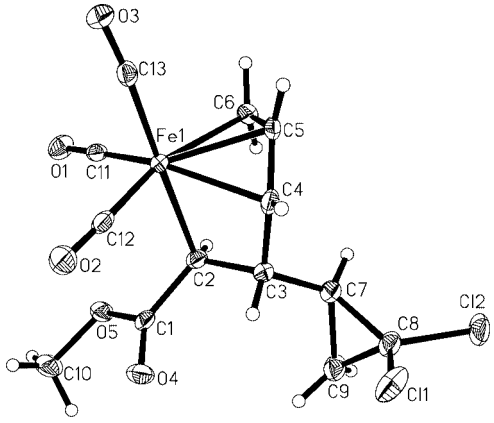


Figure 2. ORTEP diagram of **7**.

stereomeric cyclopropanes **8** and **9** (4.5:1). The relative stereochemistry of the major diastereomer **8** was assigned on the basis of the X-ray crystal structure of its *p*-nitrobenzoate **10** (Figure 3).[9]

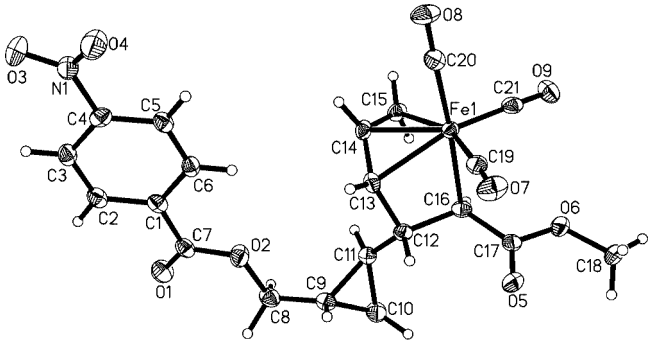
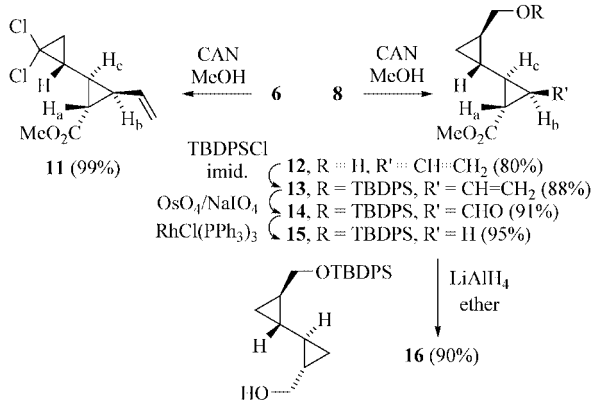


Figure 3. ORTEP diagram of **10**.

The stereoselectivity of the cyclopropanation reactions may be rationalized on the basis of approach of either dichlorocarbene or the Zn-carbenoid species on the less hindered face of the olefin (cf. inset in Scheme 2). Notably, the X-ray crystal structure of the parent 2-vinylpentenediyl complex **4a** has the vinyl group (C11–C12) alligned nearly parallel to the C6–C7 bond (dihedral angle 0.5°).[5b]

Oxidative decomplexation of either **6** or **8** with ceric ammonium nitrate (CAN) gave the bi(cyclopropyl)s **11** or **12**, each as a single diastereomer (Scheme 3). The relative stereochemistries about the trisubstituted cyclopropane rings of **11** and **12** were assigned on the basis of their ^{1}H NMR spectral data. In particular, the signals for H_a, H_b, and H_c of **11** appear at δ = 1.90 (t, J = 4.8 Hz), 2.26 (br. dt, J = 4.8, 8.1 Hz), and 1.52 (td, J = 4.5, 8.1 Hz) ppm, respectively, while for **12** these appear at δ = 1.61 (t, J = 4.5 Hz), 2.18 (dt, J = 4.4, 9.0 Hz), and 1.45 (td, J = 4.8, 9.3 Hz) ppm, respectively. These couplings are consistent with the methoxycarbonyl substituent being *trans* with respect to the vinyl and cyclopropane substituents, and this is consistent with an oxidatively induced reductive elimination process in which the stereochemistry at the metal-bonded carbon atoms is retained.[4a]



Scheme 3. Preparation of bi(cyclopropyl)s.

Protection of the primary alcohol of **12**, followed by dihydroxylation/glycol cleavage yielded the aldehyde **14**. Decarbonylation[11] of **14** with $RhCl(PPh_3)_3$ proceeded in excellent yield to afford **15**. Finally, ester reduction gave the known monoprotected bi(cyclopropyl) **16**. The spectroscopic data obtained for *rac*-**16** is consistent with the literature values.[7c]

Conclusions

Cyclopropanation of (2-alkenylpentenediyl)iron complexes **4a** and **4c** proceeds with modest diastereoselectivity. The diastereomeric cyclopropanes may be separated, and oxidative removal of iron leads to stereodefined bi(cyclopropyl)s.

Supporting Information (see also the footnote on the first page of this article): Experimental details and spectroscopic data for the cyclopropanation and decomplexation reactions.

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