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Synthesis of Cyclopropanes via Organoiron Methodology: Preparation and Rearrangement of Divinylcyclopropanes

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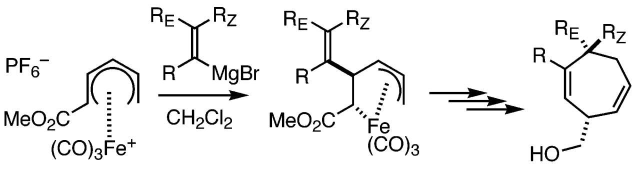
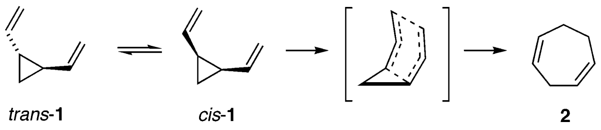
ABSTRACT



Addition of alkenyl Grignard reagents to (1-methoxycarbonylpentadienyl)iron(1+) cation generates the corresponding (2-alkenylpent-3-en-1,5-diyl)iron complexes. Oxidatively induced-reductive elimination of these complexes gives divinylcyclopropanes which can undergo subsequent Cope rearrangement to give 1,4-cycloheptadienes.

The Cope rearrangement of *cis*-divinylcyclopropane (*cis*-**1**), which occurs at <35 °C, is known to afford 1,4-cycloheptadiene (**2**, Scheme 1).[1] A variety of methods exist for the preparation of divinylcyclopropanes. Among these are oxosulfonium ylide cyclopropanation of enals followed by Wittig olefination of the resultant cyclopropanecarboxaldehyde,[2] reaction of 2-metalated vinylcyclopropanes with 3-alkoxy-2-cycloalken-1-ones followed by hydrolysis/dehydration,[3] and rhodium-catalyzed cyclopropanation of vinyldiazomethanes.[4]

Scheme 1



The addition of stabilized carbon nucleophiles to (1-methoxycarbonylpentadienyl)iron(1+) cation (**3**) is known to afford stable (pentenediyl)iron complexes (**4**), which undergo oxidatively induced-reductive elimination to give vinylcyclopropanecarboxylates (**5**, Scheme 2).[5] We have utilized this methodology to prepare 2-(2′-carboxycyclopropyl)glycines (**6**)[5a] and the C9−C16 alkenyl cyclopropane segment (**7**) of ambruticin.[5b] We herein report on the

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[1] (a) Brown, J. M.; Golding, B. T.; Stofko, J. J., Jr. *J. Chem. Soc., Chem. Commun.* **1973**, 319−320. (b) Arai, M.; Crawford, R. J. *Can. J. Chem.* **1972**, *50*, 2158−2162. (c) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. In *Organic Reactions*; Paquette, L. A., Editor-in-Chief; John Wiley & Sons: New York, 1992; Vol. 41, pp 1−133. (d) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Editor-in-Chief; Pergamon Press: New York, 1991; Vol. 5, pp 971−998.

[2] Marino, J. P.; Kaneko, T. *Tetrahedron Lett.* **1973**, 3975−3978.

[3] (a) Marino, J. P.; Browne, L. J. *Tetrahedron Lett.* **1976**, 3245−3248. (b) Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976**, *41*, 3490−3491. (c) Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205−2208.

[4] (a) Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930−936. (b) Cantrell, W. R., Jr.; Davies, H. M. L. *J. Org. Chem.* **1991**, *56*, 723−727. (c) Davies, H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817−3824. (d) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203−5223.

[5] (a) Yun, Y. K.; Godula, K.; Cao, Y.; Donaldson, W. A. *J. Org. Chem.* **2003**, *68*, 901−910. (b) Lukesh, J. M.; Donaldson, W. A. *Chem. Commun.* **2005**, 110−112. (c) Motiei, L.; Marek, I.; Gottleib, H. E.; Marks, V.; Lellouche, J.-P. *Tetrahedron Lett.* **2003**, *44*, 5909−5912.

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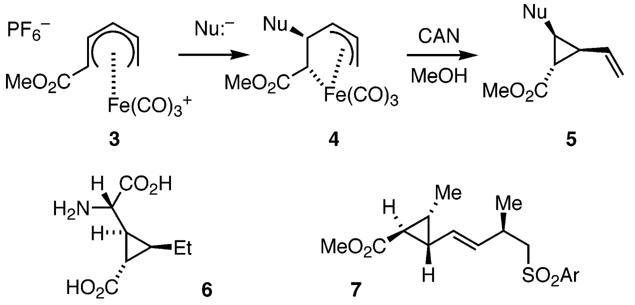
Scheme 2



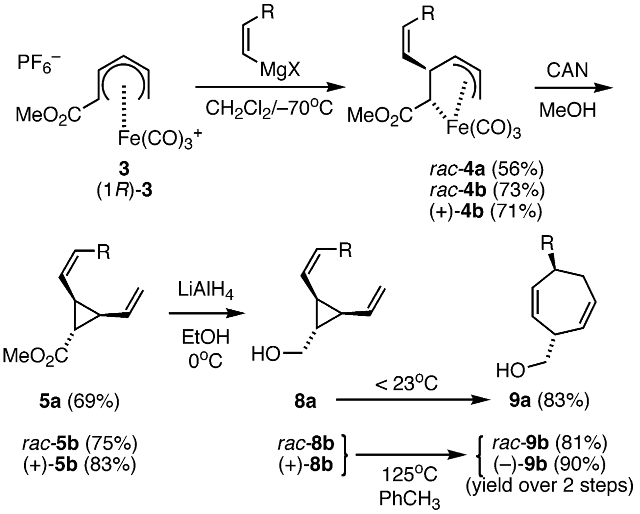
preparation and rearrangement of divinylcyclopropanes via this methodology.

Reaction of cation **3** with vinylmagnesium chloride, in CH_2Cl_2, gave the corresponding (2-alkenyl-3-pentene-1,5-diyl)iron complexes **4a** (Scheme 3). Use of CH_2Cl_2 as solvent is crucial for addition of Grignard reagents at C2; use of 1,2-dichloroethane, toluene, THF, dioxane, or mixtures led to diminished yields of **4a**. The structure of pentenediyl complex **4a** was assigned on the basis of its NMR spectral data. In particular, a ^{13}C NMR signal at δ 11.4 ppm and a ^{1}H NMR signal at δ 0.24 (d) ppm are characteristic of a carbon σ-bonded to iron and its attached proton.[5]

Oxidative decomplexation of **4a** with excess CAN/methanol gave *cis*-divinylcyclopropane **5a**. This compound rearranges at 40−60 °C to give the known (3-methoxycarbonyl)-1,4-cycloheptadiene.[6] Alternatively, reduction of the cyclopropanecarboxylate (LAH/ether) gave the rearranged (2,6-cycloheptadien-1-yl)methanol **9a**. Presumably, the intermediate divinylcyclopropane **8a** rapidly rearranges at <23 °C. It is known that the presence of an electron-withdrawing group strengthens the distal cyclopropane ring bond, and this should have an effect on the rate of the Cope rearrangement.

In a similar fashion, reaction of *rac*-**3** with the Grignard reagent prepared from *cis*-1-propenyl bromide gave *rac*-**4b**. Oxidative decomplexation of **4b** gave *rac*-**5b**, which upon reduction gave the cyclopropylcarbinol *rac*-**8b**. In comparison to the parent divinylcyclopropane **8a**, the *cis*-alkenyl cyclopropane **8b** is stable at ambient temperatures and only rearranges at elevated temperature (125 °C) to give a single cycloheptadiene *rac*-**9b**.[7] This methodology can be extended to the enantioselective preparation of cycloheptadienes. Thus reaction of (1*R*)-**3**[8] with *cis*-1-propenyl Grignard reagent gave (+)-**4b**, which upon oxidative decomplexation gave the optically active divinylcyclopropane (+)-**5b**. Reduction of (+)-**5b** gave (+)-**8b** which, upon rearrangement at elevated temperature, gave (−)-**9b**. Both (+)-**4b** and (+)-**5b** were determined to be >95% ee on the basis of ^{1}H NMR spectroscopy in the presence of a chiral lanthanide shift reagent, while the (*S*)-Mosher's ester of (−)-**9b** was determined to be >95% de.

Scheme 3[a]



[a] **a**, R = H; **b**, R = Me.

In a similar fashion, reaction of **3** with the Grignard reagents derived from 2-bromo-1-propene, α-bromostyrene, 1-bromo-2-methylpropene, and 1-bromocyclopentene gave the corresponding (pentenediyl)iron complexes **4c**−**f** (Table 1). Oxidative decomplexation of **4c** gave the divinylcyclopropane **5c** along with the rearranged cycloheptadiene product (ca. 2.5:1, 88% yield). Reduction of this mixture gave the (2,6-cycloheptadien-1-yl)methanol **9c** (Cope rearrangement occurs at <23 °C). In comparison, oxidative decomplexation of (pentenediyl)iron complexes **4d** or **4e**, which contain an electron-rich alkenyl group, gave diminished yield of divinylcyclopropane. Further experimentation indicated that this diminished yield was due to secondary oxidation of the divinylcyclopropane product by CAN. For this reason, we explored alternative oxidation conditions, the most successful of which was the use of alkaline hydrogen peroxide at low temperature (conditions B). While the chemical yields under conditions B were good, the products consisted of a mixture of *cis*- and *trans*-divinylcyclopropanes, as evidenced by NMR spectroscopy. These mixtures could be converted into a single cycloheptadiene product by the standard reduction/Cope rearrangement conditions. Monitoring of this reaction by VT NMR spectroscopy indicated that the *cis*-divinylcyclopropane rearranges at temperatures lower than those of the trans isomer; rearrangement of the trans isomer presumably occurs via isomerization to the cis isomer via a diradical opening of the cyclopropane ring.[1]

Generation of the mixture of *cis*- and *trans*-divinylcyclopropanes (**5**/**5′**) is rationalized due to the difference in the oxidizing agent involved. For the (pentenediyl)iron complex **4e** (Scheme 3), treatment with CAN is presumed to involve single electron oxidation to afford a 17e$^-$ intermediate, which undergoes rapid reductive elimination to give the *cis*-divinylcyclopropane **5e**. Alternatively, treatment of **4e** with alkaline hydrogen peroxide proceeds via nucleophilic attack

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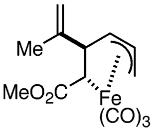
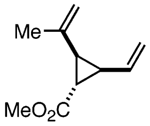
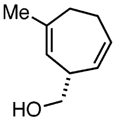
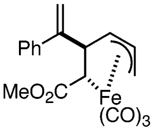
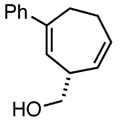
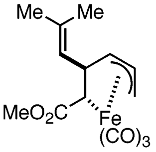
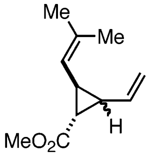
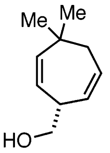
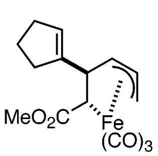
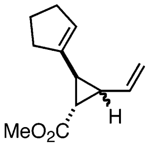
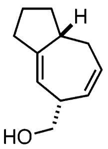
(6) Pikulik, I.; Childs, R. F. *Can. J. Chem.* **1977**, *55*, 251−258.

(7) The higher temperature for Cope rearrangement of divinylcyclopropanes possessing a *cis*-alkenyl group reflects the boatlike transition state for this [3.3] sigmatropic rearrangement: Schneider, M. P.; Rau, A. *J. Am. Chem. Soc.* **1979**, *101*, 4426−4427.

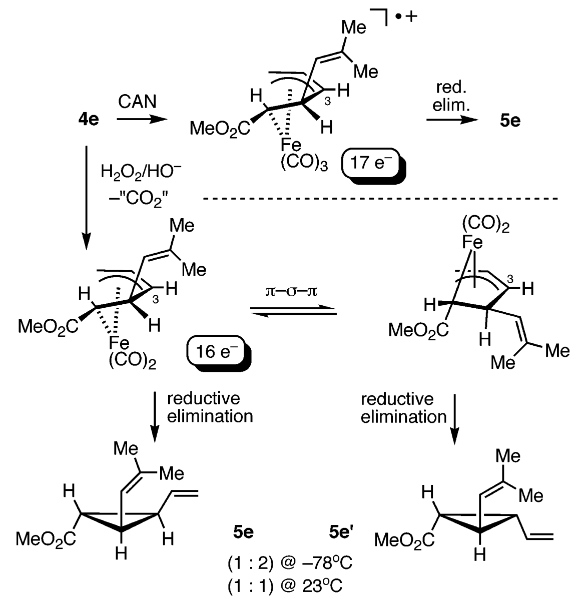
(8) For preparation of (1*R*)-**3** see: Tao, C.; Donaldson, W. A. *J. Org. Chem.* **1993**, *58*, 2134−2143.

Table 1. Preparation of (Pentendiyl)iron Complexes, Divvinylcyclopropanes, and Cycloheptadienes

pentenediyl complex	oxidation conditions[a]	divinyl-cyclopropane	Cope conditions[a]	1,4-cyclo-heptadiene
 **4c** (42-52%)	**A**	 **5c**[c]	**C**	 **6c** (82%)[b]
 **4d** (38-49%)	**A**	not observed	**C**	 **6d** (33%)[b]
 **4e** (71-76%)	**A** **B**	 **5e** (11%, *cis* only) **5e/e'** (63-84%)[d]	**D**	 **6e** (80%)[b]
 **4f** (50%)	**B**	 **5f** (85%)[e]	**E**	 **6f** (76%)[b]

[a] Decomplexation conditions: A = excess CAN/MeOH/23 °C; B = H_2O_2/MeOH/−45 °C; C = LAH, then rearrangement at or below 23 °C; D = LAH, then rearrangement at 195 °C; E = LAH, then rearrangement at 210 °C. [b] Yield over three steps (decomplexation, LAH reduction, and Cope rearrangement). [c] Obtained as a mixture with the cycloheptadiene 2.5:1). [d] Divinylcyclopropane obtained as a mixture of cis and trans isomers (1:1). [e] Divinylcyclopropane obtained as a mixture of cis and trans isomers (ca. 1:2.5).

Scheme 4



on coordinated CO, and decarbonylation, to generate a $16e^-$ intermediate. Reductive elimination from the $16e^-$ intermediate is slower, and a competitive reaction is a $\pi-\sigma-\pi$ rearrangement that migrates the iron from one face to the opposite face of the pentenediyl ligand. Notably, the ratio of **5e**:**5e′** produced from decomplexation with H_2O_2/HO⁻ varies depending on the reaction temperature. In summary, a synthesis of divinylcyclopropanes from (pentadienyl)iron(1+) cations has been developed. The divinylcyclopropane products undergo Cope rearrangement to afford cycloheptadienes. The overall yields for this 4-step transformation (ca. 38−61%) are comparable to other literature methods and preparation of enantiomerically pure cycloheptadienes has been demonstrated. Applications of this methodology to the synthesis of hydroazulene containing natural products will be reported in due course.

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Supporting Information Available: Details of experimental procedures and characterization and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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