

## Sequential Additions of Nucleophiles to Tricarbonyl( $\eta^4$ -cycloheptadienyl)iron Tetrafluoroborate

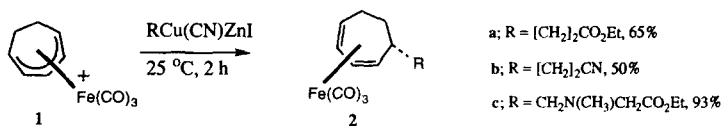
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**Abstract:** Reaction of lithium diisopropylamide (LDA) with ( $\eta^4$ -cycloheptadiene)Fe(CO)<sub>3</sub> complexes bearing functionalized side chains at C-5, under an atmosphere of carbon monoxide, gives the bridged bicyclo[4.2.1]nonane derivative **3** after acid quenching, whereas treatments of the reaction mixture with carbon electrophiles furnished the tricyclo[5.2.1.0<sup>4,8</sup>]decane derivative **7**. The iron-mediated intramolecular nucleophilic addition allows for the direct stereocontrol of six stereogenic centers of the tricyclic skeleton. Copyright © 1996 Elsevier Science Ltd

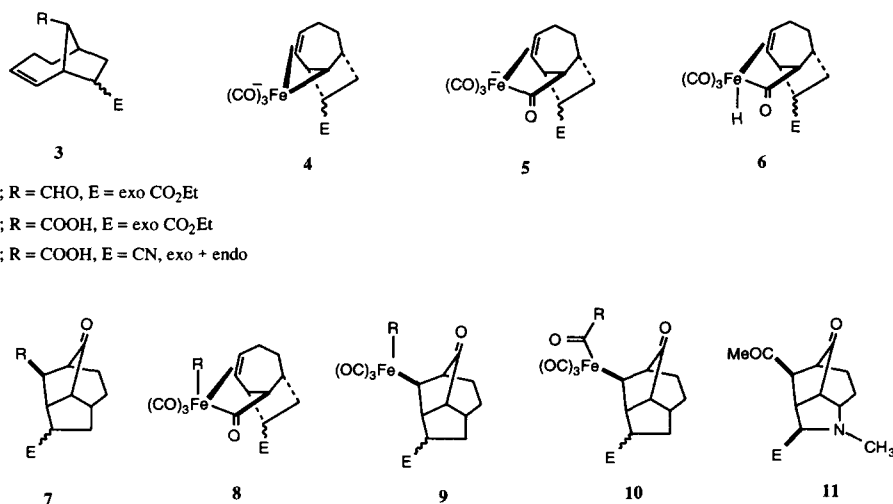
Seven-membered carbocycles are commonly used in the construction of complicated natural products.<sup>1</sup> Recently, tropone<sup>2</sup> and the troponeiron tricarbonyl complex<sup>3</sup> have been shown to be versatile building blocks for the synthesis of a variety of sesquiterpenes with the bicyclo[5.3.0]decane skeleton.<sup>4</sup> Normally, several steps starting from 1,8-addition of a protected functionalized three-carbon chain to tropone were needed to construct the bicyclo[5.3.0]decane or the perhydroazulene ring system.<sup>2</sup> Rosenblum had demonstrated that the reaction of tropyliumiron tricarbonyl cation salts with ( $\eta^1$ -allyl)Fp [Fp = C<sub>5</sub>H<sub>5</sub>Fe(CO)<sub>2</sub>] complexes gave the perhydroazulene ring system in a single step.<sup>3a,5a</sup> In addition, Helquist had reported the direct generation of a tricyclic cycloheptanone-containing system in a one-pot reaction sequence by the condensation of lithium cyclohexenolate with a cyclopropanone derivative.<sup>5b</sup> We had also shown that fused bicyclo-[5.3.0]decane and -[5.4.0]undecane ring skeletons can be easily available by intramolecular nucleophilic addition of carboester functionalized ( $\eta^6$ -cycloheptatriene)Cr(CO)<sub>3</sub> complexes. However, construction of complex bridged bicyclic and tricyclic skeletons containing the seven-membered fragment remains a continuing major challenge in synthetic organic chemistry. We now report a simple synthetic pathway to produce fairly complicated bridged bicyclo[4.2.1]nonane and tricyclo[5.2.1.0<sup>4,8</sup>]decane skeletons by sequential additions of nucleophiles to ( $\eta^5$ -cycloheptadienyl)Fe(CO)<sub>3</sub> cation **1**.

## Scheme 1



Cation **1** was prepared in a single step from ( $\eta^4$ -cycloheptatriene)Fe(CO)<sub>3</sub> and tetrafluoroboric acid following a literature procedure.<sup>7</sup> Slow addition of a THF solution of the highly functionalized zinc–copper reagents RCu(CN)ZnI (1.2 equiv.) to a stirred suspension of cation **1** in THF at 0 °C under nitrogen. The addition was carried out for 2 h at 23 °C followed by workup with saturated aqueous ammonium chloride and diethyl ether extraction. After purification by flash column chromatography on silica gel, complexes **2a–b** were obtained as the major products (**2a** 65%, **2b** 50%, Scheme 1). Complex **2c** was synthesized in 93% yield by reaction of sarcosine ethyl ester hydrochloride and cation **1** in triethylamine following a literature method (Scheme 1).<sup>8</sup> The *trans* relationship between the nucleophile and the metal moiety of complexes **2** was assigned based upon comparison of their C-5-*endo* proton chemical shift values [ $\delta$  1.93 (1H, br.s)] with the values of 5-*exo*-substituted ( $\eta^4$ -cyclohexadiene)Fe(CO)<sub>3</sub> complexes reported in the literature.<sup>9</sup> The result is consistent with our previous report for the formation of ( $\eta^4$ -cyclohexadiene)Fe(CO)<sub>3</sub> complexes with *trans* functionalized side chains at the C-5 position of the ring.<sup>10</sup> Further manipulation of the resulting complexes **2** was demonstrated as follows. Treatment of **2a** with lithium diisopropylamide (LDA, 1.2 equiv.) in THF and hexamethylphosphoramide (HMPA, THF–HMPA = 3:1) at –78 °C for 2 h under an atmosphere of carbon monoxide (14 psi) followed by quenching the reaction mixture with TFA (10 equiv.) produced the bicyclo[4.2.1]nonanecarboxylic acid derivative **3a** in 69% yield with an incorporated CO at the C-9 position. It is important to note that four new contiguous stereogenic centers of **3a** are created with extreme diastereoselectivity. The product of the relative stereochemistry as shown was isolated as a single diastereomer. The stereochemical course of **3a** is consistent an anti addition of the kinetic enolate at C-3 position of the diene ligand to give the putative homoallyl anion intermediate **4**. Carbonyl insertion was then enhanced by an external CO (14–18 psi) to generate acyliron anion intermediate **5**. Electrophilic quenching of **5** with trifluoroacetic acid produced iron–hydride species **6**, which underwent reductive elimination to give **3a**. Moreover, oxidation of **5** with molecular oxygen afforded acid **3b** as the only diastereoisomer (37% from **2a**) and a mixture of *exo* and *endo* diastereoisomers (*exo*–*endo* = 7:1) of **3c**<sup>11</sup> (53% from **2b**).<sup>12</sup> It was suggested that, for complex **2a**, only one of the diastereotopic protons at  $\alpha$ -carbon of the ester group was removed by LDA under kinetically controlled reaction conditions (–78 °C). Thus, only one diastereoisomer was isolated. Unlike an ester group, a cyano group of complex **2b** is rather small. Therefore, either one of the two  $\alpha$ -protons is possibly removed by LDA to generate both *exo* and *endo* isomers of **3c** (*via infra*).

Interestingly, the reaction underwent different pathways by quenching the reaction mixture with carbon electrophiles such as iodomethane or benzyl bromide. Thus, treatment of complex **2** with LDA (1.2 equiv.) in THF and HMPA (THF:HMPA = 3:1) under CO (14 psi) at  $-78\text{ }^{\circ}\text{C}$  for 2 h followed by quenching the reaction mixture with iodomethane or benzyl bromide gave tricyclo[5.2.1.0<sup>4,8</sup>]decanecarboxylic acid derivatives **7a** (44% from **2a**) and **7b** (10% from **2a**) as the only diastereoisomer in each case and a mixture of exo and endo isomers of **7c** (41% from **2b**, exo:endo = 7:3), respectively, in moderate yields. The formation of tricyclic skeletons was suggested as follows. Quenching the postulated anion intermediate **5** with RX (RX = MeI or PhCH<sub>2</sub>Br) produced **8**. Intramolecular alkene insertion into the iron–acyl bond of **8** would lead to the formation of the tricyclic intermediate **9**. Carbonyl insertion into the iron–carbon bond of **9** produced ironacyl intermediate **10**, which underwent reductive elimination to afford tricyclic compounds **7a–c**. Under the same reaction conditions, intramolecular cyclization of complex **2c** bearing an amino acid derivative produced heterotricyclic compound **11** as the only diastereoisomer isolated in 57% yield. Thus, the new synthetic strategy provides a convenient route to produce complicated tricyclo[5.2.1.0<sup>4,8</sup>]decane derivatives **7a–b** and **11** as a single diastereomer with six new stereogenic centers.



- a; R = CHO, E = exo CO<sub>2</sub>Et  
 b; R = COOH, E = exo CO<sub>2</sub>Et  
 c; R = COOH, E = CN, exo + endo

- a; R = COMe, E = exo CO<sub>2</sub>Et  
 b; R = COCH<sub>2</sub>Ph, E = exo CO<sub>2</sub>Et  
 c; R = COMe, E = CN, exo + endo

**Acknowledgment:** This research was supported by a grant from the National Science Council of the Republic of China (Grant No. NSC 84-2113-M-003-005).

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(Received in Japan 23 July 1996; revised 19 August 1996; accepted 20 August 1996)