

Sequential Additions of Nucleophiles to Tricarbonyl(η^4 -cycloheptadienyl)iron Tetrafluoroborate

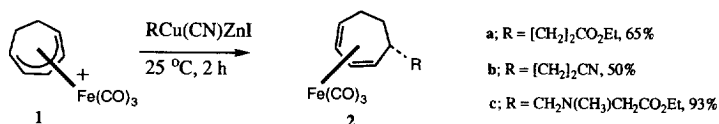
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Abstract: Reaction of lithium diisopropylamide (LDA) with (η^4 -cycloheptadiene)Fe(CO)₃ complexes bearing functionalized side chains at C-5, under an atmosphere of carbon monoxide, gives the bridged bicyclo[4.2.1]nonane derivative **3** after acid quenching, whereas treatments of the reaction mixture with carbon electrophiles furnished the tricyclo[5.2.1.0^{4,8}]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

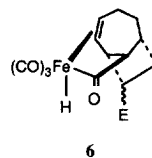
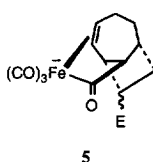
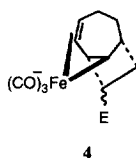
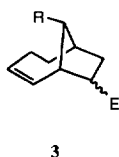
Seven-membered carbocycles are commonly used in the construction of complicated natural products.¹ Recently, tropone² and the troponeiron tricarbonyl complex³ have been shown to be versatile building blocks for the synthesis of a variety of sesquiterpenes with the bicyclo[5.3.0]decane skeleton.⁴ Normally, 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.² Rosenblum had demonstrated that the reaction of tropyliumiron tricarbonyl cation salts with (η^1 -allyl)Fp [Fp = C₅H₅Fe(CO)₂] complexes gave the perhydroazulene ring system in a single step.^{3a,5a} 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.^{5b} 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 (η^6 -cycloheptatriene)Cr(CO)₃ 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^{4,8}]decane skeletons by sequential additions of nucleophiles to (η^5 -cycloheptadienyl)Fe(CO)₃ cation **1**.

Scheme 1



Cation **1** was prepared in a single step from $(\eta^4\text{-cycloheptatriene})\text{Fe}(\text{CO})_3$ and tetrafluoroboric acid following a literature procedure.⁷ Slow addition of a THF solution of the highly functionalized zinc–copper reagents $\text{RCu}(\text{CN})\text{ZnI}$ (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).⁸ 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 [δ 1.93 (1H, br.s)] with the values of 5-*exo*-substituted $(\eta^4\text{-cyclohexadiene})\text{Fe}(\text{CO})_3$ complexes reported in the literature.⁹ The result is consistent with our previous report for the formation of $(\eta^4\text{-cyclohexadiene})\text{Fe}(\text{CO})_3$ complexes with *trans* functionalized side chains at the C-5 position of the ring.¹⁰ 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**¹¹ (53% from **2b**).¹² It was suggested that, for complex **2a**, only one of the diastereotopic protons at α -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 α -protons is possibly removed by LDA to generate both *exo* and *endo* isomers of **3c** (*via infra*).

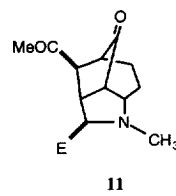
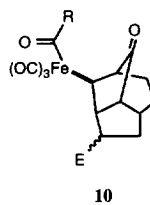
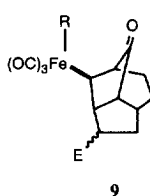
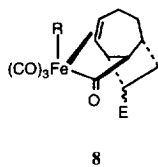
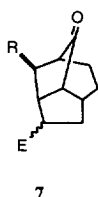
Interestingly, the reaction underwent different pathways by quenching the reaction mixture with carbon electrophiles such as iodomethane or benzyl bromide. Thus, treatment of complex **2** with LDA (1.2 equiv.) in THF and HMPA (THF–HMPA = 3:1) under CO (14 psi) at $-78\text{ }^{\circ}\text{C}$ for 2 h followed by quenching the reaction mixture with iodomethane or benzyl bromide gave tricyclo[5.2.1.0^{4,8}]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 PhCH₂Br) 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^{4,8}]decane derivatives **7a–b** and **11** as a single diastereomer with six new stereogenic centers.



a; R = CHO, E = exo CO₂Et

b; R = COOH, E = exo CO₂Et

c; R = COOH, E = CN, exo + endo



a; R = COMe, E = exo CO₂Et

b; R = COCH₂Ph, E = exo CO₂Et

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)