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A Novel Synthetic Approach to Medium Ring Lactones via Dienetricarbonyliron Complexes

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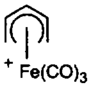
***Abstract*:** Reaction of lithium diisopropylamide (LDA) with (η^4-1,3-buadiene)$Fe(CO)_3$ complexes bearing carboester functionalized side chains at C-5 gives eight- to ten-membered lactones as the major products after electrophilic quenching. However, treatments of the complexes with LDA, under an atmosphere of carbon monoxide, furnish bridged bicyclo[5.2.1]decane and bicyclo[6.2.1]undecane lactone skeletons as the major products. Copyright © 1996 Elsevier Science Ltd

Medium-sized (eight- to twelve-membered) lactones and cyclic ethers constitute the characteristic molecular fragment of numerous natural products of biological interest, e.g. brevetoxin A,[1] laurencin,[2] laurenyne,[3] octalactin A,[4] octalactin B,[4] decan-9-olide,[5] and (*Z*)-dec-4-en-9-olide.[5] The most widely used method for the synthesis of medium-sized lactones involves intramolecular cyclization of a hydroxy and a carboxylic acid functionality (esterification),[6] Bayer-Villiger oxidation of seven-membered ring ketones,[7] Claisen rearrangement of a vinyl ketal to an eight-membered ring lactone,[8] or an atom transfer cyclization to eight- and nine-membered lactones.[9] However, only few reports on the preparation of medium-sized lactones promoted by transition metals. Of these reactions, however, formation of macrocyclic lactones has so far been restricted to the Stille coupling reaction.[10] We report here a novel method for the construction of medium-sized lactones via intramolecular cyclization of (η^4-1,3-diene)$Fe(CO)_3$ complexes bearing carboester functionalities at the terminal position of the diene ligand.

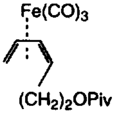
To prepare the starting carboester functionalized (η^4-1,3-diene)$Fe(CO)_3$ complexes, we adopted the well-known strategy developed by Birch and Pearson.[11] Treatment of cation **1** with zinc–copper reagent **2** [$PivOCH_2Cu(CN)ZnI$], prepared from pivalate iodide and zinc followed by transmetallation with $CuCN{\bullet}2LiCl$,[12] gave complex **3**. Reduction of **3** with diisobutylaluminum hydride (DIBAL) at 0 °C generated alcohol complex **4**. Acylation of **4** with acylchlorides (RCOCl, R = i-Pr or n-Pr) furnished ester complexes **5a** (88% from **1**) and **5b** (85% from **1**). Complex **6** with one more carbon unit on the side chain was synthesized in 69% yield from cation **1** and the zinc–copper reagent [$BrZn(CN)CuCH_2CO_2Et$] using the similar method.

Our intramolecular cyclization study began with complex **5a** (Scheme 1). Reaction of **5a** with 1.5 molar equiv of LDA in THF/HMPA (3:1) at –78 °C under nitrogen produced the eight-membered ring lactone **7a**

(8%) and the bridged bicyclic lactone **8** (20%) with an incorporated CO at the C-8 position after acid quenching. It is important to mention that lactones **7a** and **8** resulted from anti addition of the ester enolate at the internal position (C-2) of the diene ligand and no addition at C-3 was found. Unlike our previous reports, intramolecular nucleophilic additions of ester enolate to (η^4-1,3-diene)Fe(CO)$_3$ complexes with 3 or 4 atom side chains occurred exclusively at the C-3 position of the diene ligand.[13] Thus, a longer side chain allows the ester enolate to attack at the internal position (C-2) of the diene ligand to generated the postulated homoallyl anionic intemediate **9**. Protonation of **9** generated iron–hydride species **10**. Reductive elimination of **10** gave **7a** (path a). However, intramolecular alkene insertion into the iron–hydride bond of **10**, followed by CO insertion and reductive elimination produced **8** (path b).[14] Thus, the addition was performed under an atmosphere of carbon monoxide (14 psi), which increased the yield of **8** to 39% as the only product isolated. The same reaction mixture could be quenched with molecular oxygen or iodomethane to furnish acid derivative **7b** (31%) and methyl ketone derivative **7c** (15%), respectively, as the only product in each case. None of the bridged bicyclic lactones, such as **8** was isolated.



1



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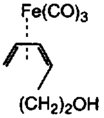

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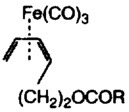
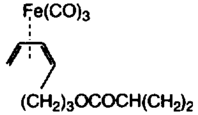


5

a: R = i-Pr

b: R = n-Pr



6

However, under thermally controlled reaction conditions (25 °C), intramolecular cyclization of **5a** using 1.5 molar equiv of LDA generated nine-membered ring lactones **11** and **12** in a 3:4 ratio in 39% yield. Lactones **11** and **12** derived from addition of the ester enolate at the less hindered terminal position (C-1) of the diene ligands agrees closely with the formation of more stable (η^3-allyl)Fe(CO)$_3$ anions from intermolecular additions of carbon nucleophiles to (η^4-1,3-diene)Fe(CO)$_3$ complexes under thermally controlled reaction conditions.[15] Quenching the postulated allyl anion species **13** with acid afforded nine-membered lactones **11** and **12**. Under the same reaction conditions, intramolecular cyclization of complex **5b** gave the eight-membered ring lactone **14a** and the bridged bicyclic lactone **15** as a diastereomeric mixture in each case at –78 °C after acid quenching (**14a**/**15** = 2 : 1 , 61% overall yield, entry 1, Table 1). The same reaction mixture was quenched with molecular oxygen to produce eight-membered ring lactone **14b**[16] as a mixture of diastereoisomers (*trans/cis* = 3:1, entry 2, Table 1). Moreover, intramolecular cyclization of **5b** under thermally controlled reaction conditions (25 °C) produced nine-membered ring lactones **16** and **17** in 2:1 ratio in 44% overall yield (entry 3, Table 1).

Increasing the tether length by one with complex **6** (entries 4–6, Table 1), also underwent intramolecular cyclization in the similar way to produce nine-membered ring lactone **18** as the major product (25%) and a trace amount of the bridged bicyclic lactone **19** at – 78 °C (entry 4, Table 1).The yield of **19** (18%) could be increased by introducing an atmosphere of CO before acid quenching (entry 5, Table 1). As expected, intramolecular cyclization of **6** at 25 °C generated ten-membered ring lactone **20** in 8% yield (entry 6, Table 1).

Scheme 1

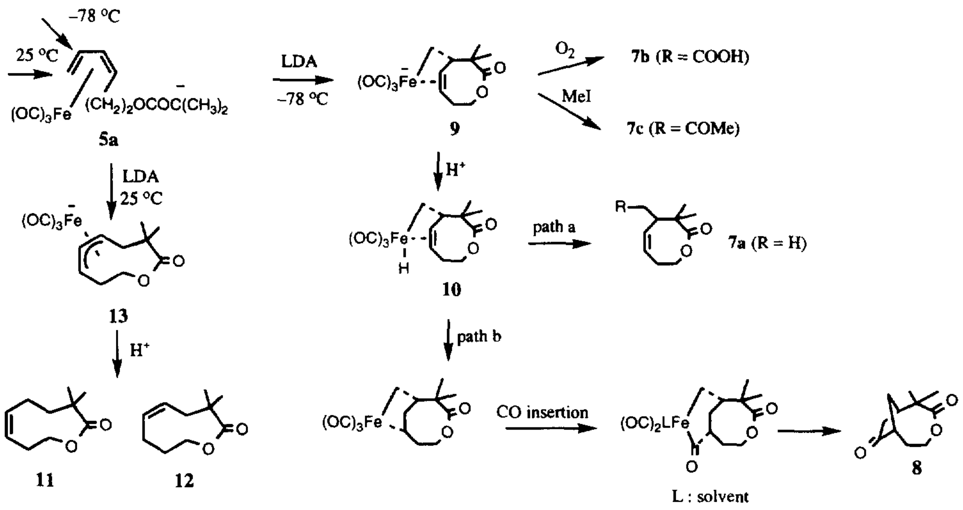
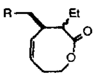
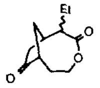
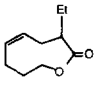
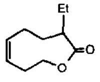
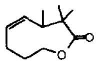
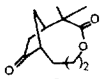
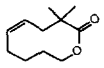


Table 1. Intramolecular cyclization and electrophilic quenching of complexes 5 and 6.

Entry	starting complexes	conditions	electrophiles	Product	yield
1	**5b**	– 78 °C	H$^+$	 **14a** (R = H)  **15**	61%
2	**5b**	– 78 °C	O$_2$/H$^+$	**14b** (R = COOH)	36%
3	**5b**	25 °C	H$^+$	 **16**  **17**	44%
4	**6**	– 78 °C	H$^+$	 **18**  **19** trace	25%
5	**6**	– 78 °C / CO	H$^+$	**19**	18%
6	**6**	25 °C	H$^+$	 **20**	8%

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16. Rigorous proof of the structures of **7b** and *trans* **14b** were accomplished by X-ray diffraction analysis.

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