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Diastereofacially Selective Enolate Claisen Rearrangements of [4-7-η^4-(1-Acyloxy-2,4,6-octatrienyl)]tricarbonyliron Complexes

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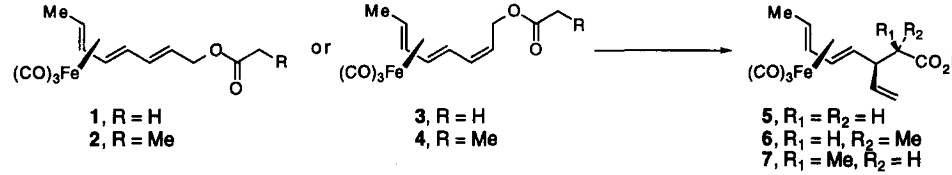
Abstract: The enolate Claisen rearrangements of 1-4 exhibit very high diastereofacial selectivity with the developing C-C bond forming anti to the -Fe(CO)$_3$ substituent. Copyright © 1996 Elsevier Science Ltd

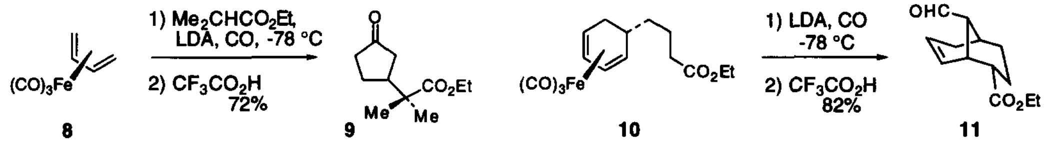
η^4-Diene iron(tricarbonyl) complexes have found numerous applications in organic synthesis.[1-3] Of particular interest is the ability of the iron(tricarbonyl) unit to control the stereochemistry of a wide range of nucleophilic additions or cycloadditions to adjacent carbonyl groups, double bonds, or cationic centers.[1,4-7] In connection with a current problem in natural products synthesis,[8] we became interested in the possibility that the -Fe(CO)$_3$ unit could control the diastereofacial selectivity of Claisen rearrangements of trienylic esters like **1-4**.[9] We were of course aware of the fact that η^4-diene iron(tricarbonyl) complexes are susceptible to nucleophilic attack by a variety of organometallic nucleophiles, including enolates;[10-14] two illustrative examples are provided by the conversions of **8** to **9**[11] and **10** to **11**.[13] However, the literature also contained several reports indicating that enolates conjugated to diene-Fe(CO)$_3$ units could be generated and used in alkylation reactions.[15-18] Therefore, we were hopeful that conditions could be developed to permit the enolate Claisen rearrangements of **1-4**[19] to proceed as planned.[20-22]



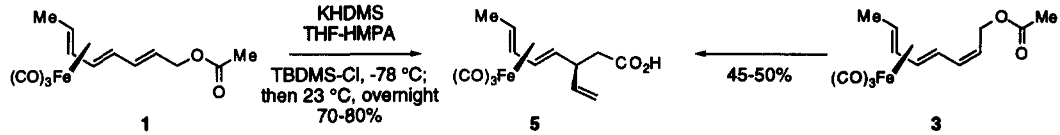
1, R = H
2, R = Me

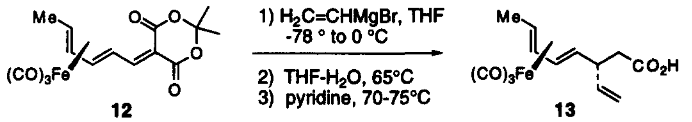
3, R = H
4, R = Me

5, R$_1$ = R$_2$ = H
6, R$_1$ = H, R$_2$ = Me
7, R$_1$ = Me, R$_2$ = H

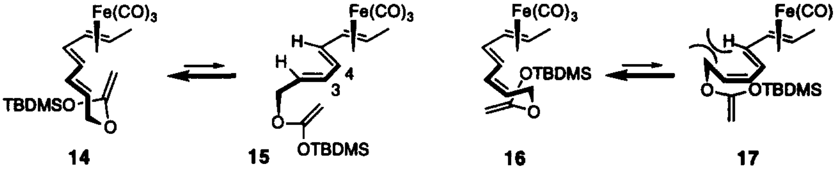


In initial experiments, sequential treatment of acetate derivative **1** with LDA and TBDMS-Cl in THF at -78 °C with warming to ambient temperature overnight provided carboxylic acid **5** in low yield (≤ 20%) following the usual acidic workup.[23] We were unable to develop a synthetically useful procedure by using lithium amide bases (LDA, LiTMP, LHMDS)[24] in a variety of solvents (THF, Et$_2$O, with or without HMPA or DMPU as additives) with various electrophilic trapping agents (TMS-Cl, TMS-OTf, TBDMS-Cl, TBDMS-OTf, or (EtO)$_2$P(O)Cl[25]). The majority of these experiments provided a complex mixture of products. However, a successful protocol was devised which involved use of 1.05-1.15 equiv. of KHMDS in THF with 23% HMPA as cosolvent and 1.2 equiv. of TBDMS-Cl as an internal silylating agent.[26] Under these conditions, carboxylic acid **5** was obtained as a *single diastereomer* in 70-80% yield from **1**, and in 45-50% yield from **3**; diastereomer **13** was not detected in the crude reaction mixtures. Use of larger quantities of KHMDS led to a substantial decrease in yield. The stereochemistry of **5** was assigned by comparison with **13**, which was prepared by addition of H_2C=CHMgBr to the sorbaldehyde-derived alkylidene malonate complex **12**.[7]



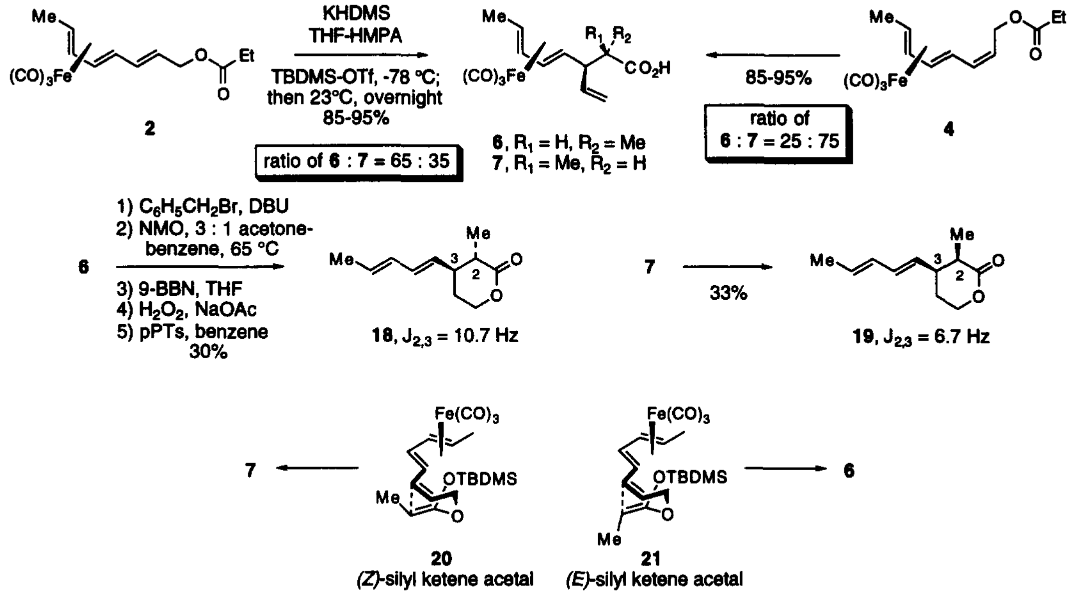


These results indicate that the Claisen rearrangements of the ketene silyl acetals derived from **1** and **3** proceed by way of transition structures **14** and **16**, respectively, with the new C-C bond developing anti to the -Fe(CO)3 group. Claisen rearrangement by way of the alternative conformations **15** or **17** would lead to diastereomer **13**, which was not observed. At the outset, we had anticipated that the Claisen rearrangement of the (Z)-allylic acetate **3** would be highly diastereofacially selective with respect to the diene-Fe(CO)3 unit, since the severe 1,5-interaction present in **17** should raise the energy of this transition structure relative to **16**. It is remarkable that very high stereoselectivity was also observed in the Claisen rearrangement of **1** (via **14**), since we expected that transition structure **15** with an s-cis conformation about the C(3)-C(4) bond should be reasonably accessible. The factors that cause this reaction to proceed virtually exclusively by way of **14** are not clear at present.



The enolate Claisen rearrangement of propionates **2** and **4** gave best results (both yield and diastereoselectivity) when performed with TBDMS-OTf rather than TBDMS-Cl as the internal silylating agent. However, in contrast to the excellent results obtained with **1** and **3**, the reactions of **2** and **4** provided inseparable mixtures of diastereomeric acids **6** and **7** (ca. 2 : 1 from **2** and 1 : 3 from **4**) in 85-95% yield. The stereochemistry of the two products was assigned by conversion to the diastereomeric lactones **18** and **19**. Treatment of the mixtures of **6** and **7** with $C_6H_5CH_2Br$ and DBU in CH_3CN provided the corresponding benzyl esters which were separated by careful chromatography (72%). Decomplexation of the diene-Fe(CO)3 units by using NMO in acetone-benzene at 65 °C (85-92%),[27] followed by selective hydroboration of the vinyl groups with 9-BBN (52-53%)[28] and treatment of the δ-hydroxy esters with pyridinium *p*-toluenesulfonate in benzene (>95% yield) provided lactones **18** and **19**. The modest diastereoselectivity of these reactions is due to poor control of the enolate geometry during the enolization step, as indicated by the following experiment. Treatment of **4** with 1.05 equiv. of KHMDS in THF-HMPA (23%) at -78 °C in the presence of TBDMS-Cl provided a 72 :

28 mixture of silyl ketene acetals **20** and **21** as determined by low temperature NMR analysis of an aliquot of the reaction mixture. Upon warming this mixture to 23 °C overnight, a 71 : 29 mixture of **7** and **6** was obtained following acidic workup (85% yield). The poor selectivity in the enolization step is most surprising, particularly since we observed that under identical conditions (KHMDS, TBDMS-Cl, THF, HMPA (23%), -78 °C), ethyl propionate was converted into the corresponding (Z)-silyl ketene acetal with high selectivity (≥90 : 10 by ^{1}H NMR analysis).[21] In any event, these results suggest that chair-like transition states are involved in the Claisen rearrangements of the propionate derived ketene silyl acetals (e.g., **20** and **21**). Although we did not rigorously establish the stereochemistry of these reactions with respect to the diene-Fe(CO)$_3$ unit, it is reasonable to assume based on the results with **1** and **3** that the developing C-C bond forms anti to the -Fe(CO)$_3$ group.



In summary, we have established that ester enolate Claisen rearrangements of diene-Fe(CO)$_3$ substituted allylic esters **1-4** can be performed in preparatively useful yields,[29] and that the -Fe(CO)$_3$ substituent exerts a strong diastereofacial bias on the stereochemistry of the developing C-C bond. Further applications of diene-Fe(CO)$_3$ complexes in organic synthesis will be reported in due course.

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(23) All new compounds were fully characterized by ^1H and ^{13}C NMR, IR, and high resolution mass spectrometry. In addition, satisfactory C,H combustion analytical data were obtained for all compounds except for **13**, **18**, and **19**.

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(29) A typical experimental procedure follows. *Best results were consistently obtained when all reagents and solvents were highly purified immediately before use.* Propionate ester **2** (103 mg, 0.32 mmol) and activated, crushed 4 Å molecular sieves (56 mg) were stirred at room temperature under N_2 in a mixture of dry THF (5.2 mL) and HMPA (freshly distilled, 1.3 mL) for 30 min. The solution was cooled to -78 °C, then TBDMS-OTf (freshly distilled, 81 µL) was added to the vigorously stirred solution, followed approximately 3 min later by KHMDS (790 µL, 0.47 M in toluene, 0.37 mmol, 1.15 equiv). The cooling bath was removed 1 min after the KHMDS addition, and the reaction mixture was allowed to warm to room temperature quickly. After being stirred overnight at room temperature, the mixture was diluted with 2 mL of Et_2O and 6 mL of a 1 M HCl solution in brine. This heterogeneous mixture was stirred vigorously for 10 min. The layers were separated, and the organic layer was washed with 1 M HCl in brine (3 x 5 mL). The aqueous layers were extracted with Et_2O (1 x 5 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and purified by flash chromatography (gradient from 5 : 1 hexanes-Et_2O to 1 : 1 hexanes-Et_2O containing 2% HOAc). A 65 : 35 mixture (^1H NMR analysis) of acids **6** and **7** was isolated as a yellow solid (97 mg, 94% yield).

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