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Chiral η^4-Butadiene-Fe(CO)$_3$ Complexes for Organic Synthesis: Reactions of (η^4-2-Alkoxy-4-vinyl-2,5-dihydrofuran)-Fe(CO)$_3$ Derivatives

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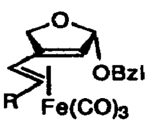
Abstract: Treatment of (η^4-2-alkoxy-4-vinyl-2,5-dihydrofuran)-Fe(CO)$_3$ complexes **1** and **2** with nucleophiles in the presence of Lewis acids leads to *exo*-products of type **4** with high diastereoselectivity. Acidic hydrolysis gives hydroxy aldehyde complexes **3**. Racemization, which seems to occur at the stage of intermediary cations of type **5**, can be suppressed by proper choice of reaction conditions.

The use of chiral diene-Fe(CO)$_3$ complexes as synthetic building blocks has found notable application in organic synthesis in recent years[1], and the search for new selective methods for the preparation[2] and transformation[3] of such complexes still remains an attractive task. In the preceding paper[4] we report on the synthesis and configurational assignment of (enantiomerically pure) complexes **1a**, **1b**, **2a** and **2b**. We herein describe some transformations of these complexes, in particular nucleophilic reactions at the acetal center leading to products of type **3** and **4**, respectively.



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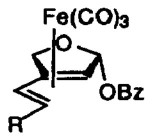

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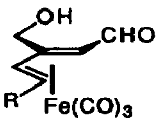

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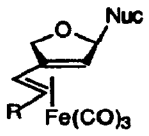

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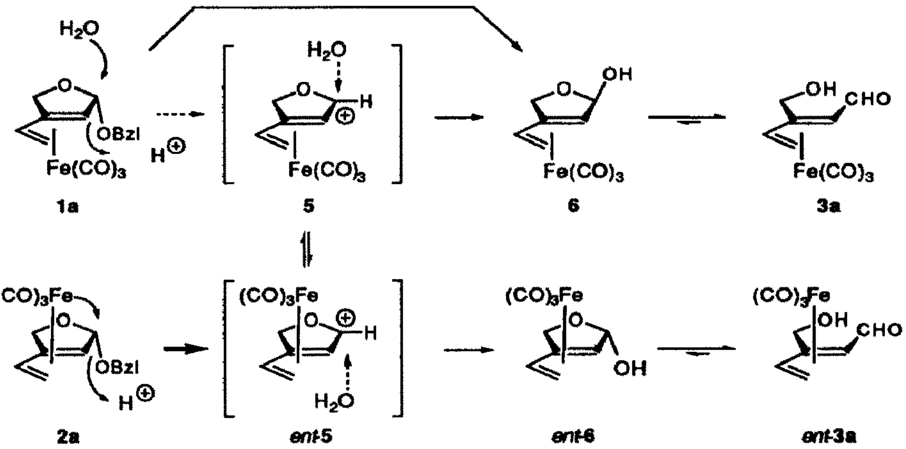
a: R = H
b: R = CO$_2$Et

Treatment of the complexes **1a** and **2a** with 1N aqueous HCl in THF at 50 °C affords the hydroxy aldehyde complexes **3a** (98±1% e.e.)[5] and *ent*-**3a** (94±3% e.e.)[5], respectively, in almost quantitative yield[6,7] (see Figure 1 for the CD spectra). The rate of hydrolysis is strikingly different for the two compounds: While the conversion of the *exo*-complex **2a** is complete within 15 min, the reaction of the *endo*-complex **1a** requires ca. 5 h under the same conditions. As preliminary experiments had shown, an almost racemic product (*ent*-**3a**; ≤ 7% e.e.)[8] is obtained from **2a** when the hydrolysis is carried out at 20 °C for 24 h (also employing 1N aqueous HCl in THF). The formation of **3a** from **1a** under these (not optimized) conditions occurs with significantly less racemization (ca. 92% e.e.)[8].

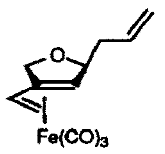
These observations can be explained in terms of the following picture (Scheme 1): The rapid reaction of the *exo*-complex **2a** is a consequence of a neighbouring-group effect of the Fe(CO)$_3$-unit which helps the benzyloxy group leaving the molecule[9]. The cation (*ent*-**5**) thus formed is than attacked by a water nucleophile giving the hemiacetal form (*ent*-**6**) of the hydroxy aldehyde *ent*-**3a**. In contrast, the formation of the cation **5** from the *endo*-complex **1a** (without any neighboring-group participation) is comparatively slow and the direct nucleophilic (S_N2-type) substitution of the benyloxy group of **1a** becomes the dominant pathway. *The racemization is likely to occur at the stage of the intermediary cation !* This immediately would explain why the loss of absolute stereochemical information is always greater when the *exo*-complex **2a** is used as the starting material. The fact that the hydrolysis of both complexes (**1a**, **2a**) proceeds at 50 °C with much less racemization, can be rationalized with the assumption, that the intermediary cations **5** and *ent*-**5**, respectively, are captured faster at higher temperatures, while the racemization is not accelerated to a comparable degree.



Scheme 1

Treatment of complexes **1** and **2** with a variety of nucleophiles in the presence of Lewis acids[10] affords the substitution products in good yields (Table 1). With hydride as nucleophile, the vinyl-dihydrofuran complex **7** (or *ent*-**7**, respectively) is obtained as an almost pure enantiomer[11,12]. In the other cases, the *exo*-products (of type **8**, **9**, **10** or their respective enantiomers) are formed as the major diastereomers. This corresponds to a preferential attack of the nucleophiles at the less hindered face of the ligands (opposite to the $Fe(CO)_3$ fragment, see Scheme 1). In a typical experiment, a solution of complex **1a** and allyltrimethylsilane (3 equiv.) in CH_2Cl_2 was treated at - 20 °C with $EtAlCl_2$ (1.5 equiv.). After 45 min, the mixture was quenched with aqueous $NaHCO_3$. After extractive workup the product was purified by flash chromatography (SiO_2, hexane/EtOAc) and kugelrohr destillation to give **8** (76%) in essentially pure form[13].

7



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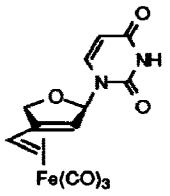

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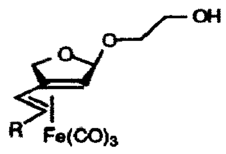

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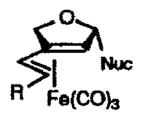
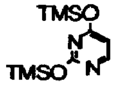


11 (Nuc = Uracil-1-yl)
12 (Nuc = OCH_2CH_2OH)

Table 1: Results of the nucleophilc substitution reactions[a)]

entry	complex	nucleophile	Lewis acid	temp. (°C)	product(s)	yield (%)	diast. ratio	e.e. (%)
1	**1a**	Et_3SiH	$EtAlCl_2$	-20	**7**	82	----	≥ 98
2	**2a**	"	$EtAlCl_2$	-20	*ent*-**7**	87	----	≥ 99
3	**1a**		$EtAlCl_2$	-20	**8**	76	> 99 : 1	≥ 99
4	**2a**	"	$EtAlCl_2$	-20	*ent*-**8**	71	> 99 : 1	≥ 99
5	**1a**		$SnCl_4$	+40	**9** + **11a**	99	95 : 5	---
6	**1a**		BF_3 x OEt_2	+35	**10a** + **12a**	84	93 : 7	---
7	**2a**	"	BF_3 x OEt_2	+35	*ent*-**10a** + *ent*-**12a**	85	92 : 8	---
8	**1b**	"	BF_3 x OEt_2	+20	**10b** + **12b**	84	90 : 10	---
9	**2b**	"	BF_3 x OEt_2	+20	*ent*-**10b** + *ent*-**12b**	76	90 : 10	---

a) All reactions were run in CH_2Cl_2; yields refer to the pure isolated products (mixtures of diastereomers in the cases of entries 5-9); the enantiomeric purities were determined (only for entries 1-4) as specified in ref.[11];

All complexes were also characterized by their CD spectra (Figure 1). The pairs of mirror-imaging curves nicely illustrate that enantiomeric products are obtained in all cases from the diastereomeric starting materials **1a** and **2a**.

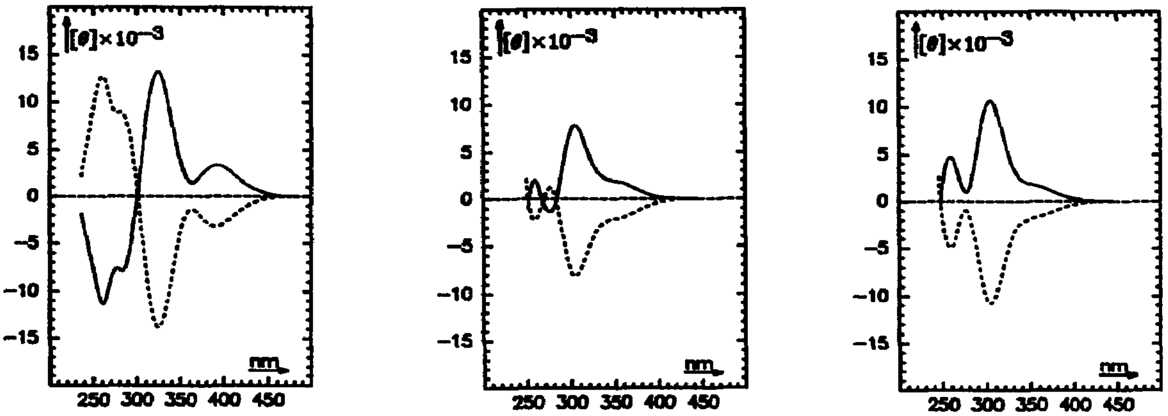


Figure 1: CD spectra in MeOH
left: **3a** (----), and *ent*-**3a** (——); middle: **7** (----), and *ent*-**7** (——); right: **8** (----), and *ent*-**8** (——)

In summary, the results presented here demonstrate that highly selective transformations can be performed at the acetal center of optically active η^4-diene-$Fe(CO)_3$ complexes of type **1** (and **2**). Racemization occurs occasionally, but can be suppressed by the proper choice of reaction conditions. An application of this chemistry for the synthesis of nucleoside analogues will be reported in due course.

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1. Selected reviews: a) Franck-Neumann, M.; in *Organometallics in Organic Synthesis*; de Meijere, A.; tom Dieck, H.; Eds.; Springer-Verlag, Berlin, **1987**; 247, b) Grée, R. *Synthesis* **1989**, 341; c) Knölker, H.-J.; *Synlett* **1992**, 371.
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3. a) Grée, D.; Grée, R.; Lowinger, T.B.; Martelli, J.; Negri, J.T.; Paquette, L.A.; *J. Am. Chem. Soc.* **1992**, *114*, 8841; b) Tao, C.; Donaldson, W.A.; *J. Org. Chem.* **1993**, *58*, 2134; c) Takemoto, Y.; Takeuchi, J.; Iwata, C.; *Tetrahedron Lett.* **1993**, *34*, 6069; d) Yeh, M.-C.,P.; Sheu, B.-A.; Fu, H.-W.; Tau, S.-I.; Chuang, L.-W.; *J. Am. Chem. Soc.* **1993**, *115*, 5941; and references cited therein.
4. Preceding paper in this issue.
5. The enantiomeric excess (e.e.) of **3** (or *ent*-**3**) was determined by HPLC on a *Daicel* Chiralcel OJ column (*n*-hexane/*i*-Pr-OH = 10 + 1.5; 0.3 ml/min).
6. All compounds were fully characterized by the usual spectroscopic methods and gave correct elemental analyses.
7. As shown by ^{1}H NMR, the equilibrium ratio between the hydroxy aldehyde **3a** and its hemiacetal form **6** is 84 : 16 in $CDCl_3$ and 79 : 21 in MeOD.
8. The e.e. was calculated in this case from the $[\alpha]_D$-values ($CHCl_3$); reference value: $[\alpha]_D^{20} = -105°$ for **3a** of 92% e.e. (HPLC).
9. Such an anchimeric assistance in reactions of related butadiene-$Fe(CO)_3$ complexes was first observed by: Clinton, N. A. and Lillya, C. P.; *J. Am. Chem. Soc.* **1970**, *92*, 3065.
10. Somehow related Lewis acid catalyzed substitutions have been described previously: Uemura, M.; Minami, T.; Yamashita, Y.; Hiyoshi, K.; Hayashi, Y.; *Tetrahedron Lett.* **1987**, *28*, 641.
11. The enantiomeric excess of compounds **7** and **8** (or their respective enantiomers) was determined by GC on a *Macherey-Nagel* FS-Hydrodex-β-PM column (25m × 0.25mm; H_2, 95 °C).
12. When the reaction (ionic hydrogenation) was carried out at higher temperatures (roomtemp.), a partial racemization was observed. Thus, **1a** gave **7** of 96% e.e. and **2a** gave *ent*-**7** with 69% e.e. under these conditions.
13. Selected data for compound **8**: ^{1}H NMR : (270 MHz, $CDCl_3$) : $\delta = -0.12$ (dd, J = 2.2 Hz, 8.6 Hz, 1H, 2'-H*anti*), 1.65 (s, 1H, 3-H), 1.66 (dd, J = 2.3 Hz, J = 6.5 Hz, 1H, 2'-H*syn*), 2.20-2.42 (m, 2H, $C\underline{H}_2CH{=}CH_2$), 4.21 (ψdt, J = 1.7 Hz, J = 6.5 Hz, 1H, 2-H), 4.51 (ψd, J = 11.4 Hz, 1H, 5-Ha), 4.82 (ψd, J = 11.4 Hz, 1H, 5-Hb), 5.06-5.08 (m,1H, $CH_2CH{=}C\underline{H}_2$(*Z*)), 5.10-5.14 (m, 1H, $CH_2CH{=}C\underline{H}_2$(*E*)), 5.50 (ψt, J = 7.6 Hz, 1H, 1'-H), 5.74-5.89 (m, 1H, $CH_2C\underline{H}{=}CH_2$); e.e.-determination (≥ 99% e.e.) as described in ref.[11]; $[\alpha]_D^{20} = -154.7$ (c = 1.0 in $CHCl_3$); CD : $\Theta(\lambda) = -4908$ (258.5 nm), - 988 (276.5 nm), - 10738 (305.0 nm), (c = 0.006 in MeOH).

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