Journal of Organometallic Chemistry, 378 (1989) 227–233
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 20024

Stereo- and enantioselectivity in catalytic hydrogenolysis of chiral substituted ferrocenes to give cyclopentanes

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(Received April 19th, 1989)

Abstract

The catalytic hydrogenolysis of 1,2-disubstituted ferrocenes having planar chirality and functional groups such as carboxyl (including ester) or tertiary amino proceeds under mild conditions (1 atm of H_2, Pd/C, CF_3COOH, 50 °C) with the retention of functional groups in the cyclopentane products. Stereoselectivity has been observed for the examples investigated, the diastereomeric ratio, *trans : cis* being close to 4 : 1, but optically inactive products are formed from the enantiomeric ferrocenes. In contrast, hydrogenolysis of enantiomeric α-(*N*,*N*-dimethylamino)ethylferrocene gives an optically active α-(*N*,*N*-dimethylamino)ethylcyclopentane with retention of configuration at the α-carbon, whose bonds are not affected during the hydrogenolysis.

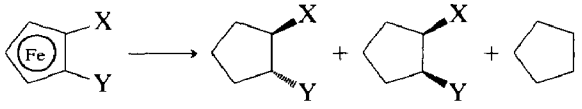
Introduction

In recent years organotransition metal derivatives have added greatly to the methods available for organic synthesis. Up to now fairly unstable derivatives with very reactive carbon–metal bonds were usually used, [1]. Another application of transition metals involves the reversible protection of some functions or the activation of a molecule by complexation to a metal group. Complexation–decomplexation has previously been used to modify the reactivity of arenes (chromiumtricarbonyl derivatives) and, to a lesser extent, that of alkynes (dicobaltcarbonyl derivatives). Development of convenient decomplexation procedures would permit use of stable organometallic α-complexes in organic synthesis, and it is desirable to find new methods for decomplexation under the mild and controlled conditions required to ensure maximum preservation of the structural features of the starting compounds.

These considerations suggest the use of derivatives of ferrocene which has high stability and an extensive chemistry. Decomplexation of ferrocenes allows the use of this class of organometallics in the synthesis of alicyclic compounds, especially

0022-328X/89/$03.50

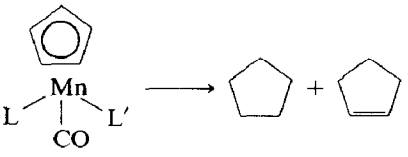
cyclopentanoids. This principle has been advanced by us previously [2]. The possibility of retaining the optical activity when planar chirality in a disubstituted ferrocene is replaced by a pair of chiral centres in the resulting cyclopentane has been also noted.



The chemistries of ferrocene and cycloalkane are completely different, so typical reactions may complement each other. Sometimes the ferrocene route may be preferable for the preparation of cyclopentanes with particular substitutents.

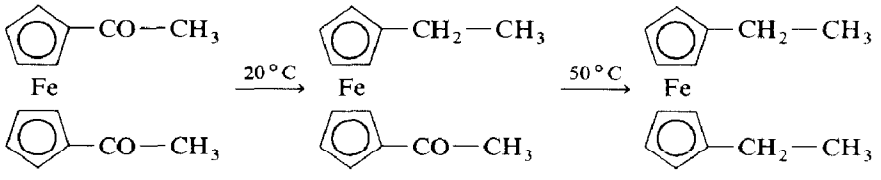
Decomplexation of cyclopentadienyl metals by catalytical hydrogenolysis

Two kinds of reactions are known which could be considered for decomplexation of ferrocene under mild conditions. These involve (i) treatment with lithium in ethylamine [3], and (ii) hydrogenation in acidic media with a Pd/C catalyst [4]. The latter reaction has been used for alkylferrocenes including ferrocenophanes [5]. This reaction is promising because we found [6] that (tertiary) amine and carboxyl (or ester) functions are unaffected under the conditions of this hydrogenolysis. Another stable π-cyclopentadienylmetal complex, cymantrene, was found to behave similarly, giving not only cyclopentane but also some cyclopentene, depending on the ligands on manganese [7].



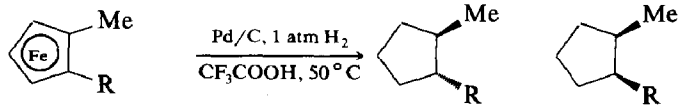
In connection with the synthesis of ferrocene analogues of prostaglandins [2,8] and subsequent conversion to natural prostanoids our attention has been mainly focused on the retention of optical activity during the hydrogenolysis. The behaviour of enantiomeric 2-methylferrocenecarboxylic acid, I, and 1-dimethylaminomethyl-2-methylferrocene, II, as well as di- and tri-substituted analogues of prostaglandins have been investigated *.

As was shown previously [6], hydroxymethylferrocene and ferrocenealdehyde are reduced at room temperature to methylferrocene, whereas hydrogenolysis with rupture of the metal–ligand bond requires 50 °C. In the present study the following standard conditions were used: 1 atm of H_2, 10% Pd/C catalyst, CF_3COOH as solvent, 50 °C. In 1,1′-diacetylferrocene the first carbonyl group is reduced at 20 °C and the second at 50 °C. No hydrogenolysis to ethylcyclopentane occurs in this case.



* For a preliminary communication see ref. 9.

Hydrogenolysis of I and II under the standard conditions in both cases gives cyclopentane and *racemic* mixtures of the diastereomeric products III and IV, respectively. Carboxyl and amino functions are retained, but the loss of optical activity suggests the involvement of achiral intermediate(s) during a multi-step process.



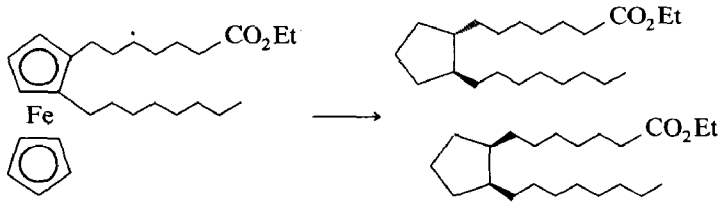
(I: R = COOH;
II: R = CH_2NMe_2)

(III: R = COOH;
IV: R = CH_2NMe_2)

The diastereomeric *trans : cis* ratio is close to 4 : 1, as determined by ^1H and ^{13}C NMR spectroscopy. Thus hydrogenolysis of 1,2-disubstituted ferrocenes takes place stereoselectively and not enantioselectively.

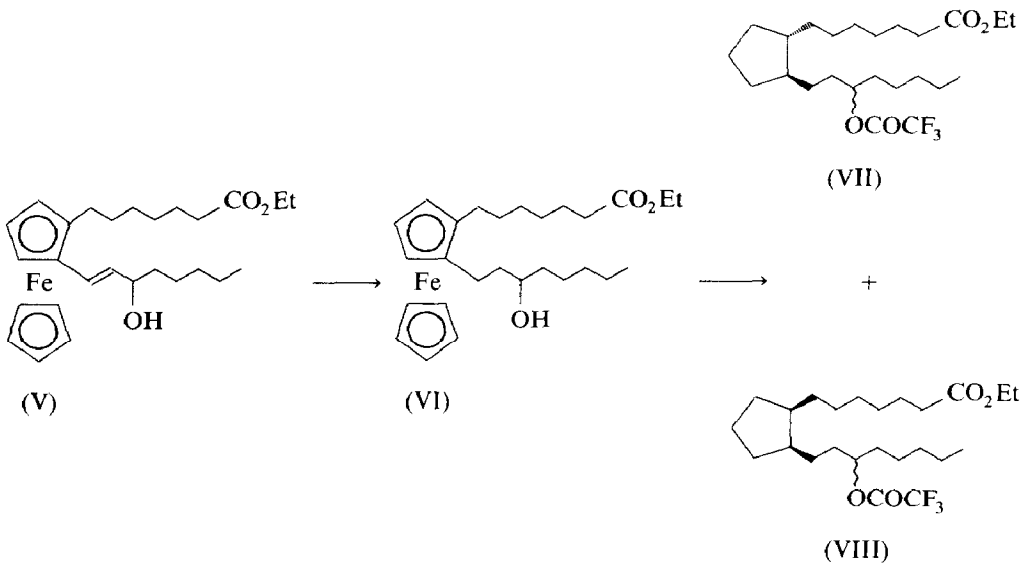
Synthesis of prostanoids by catalytic hydrogenation

The parent species for the whole family of prostanoids is prostanoic acid, *trans*-1-(6-carboxyhexyl)-2-octylcyclopentane. Hydrogenolysis of an enantiomeric precursor, 1-(6-carboxyhexyl)-2-octylferrocene [10], gives the racemic prostanoic acid admixed with approximately 20% of the *cis*-isomer, in accord with results obtained for the simpler, but related compounds I and II.

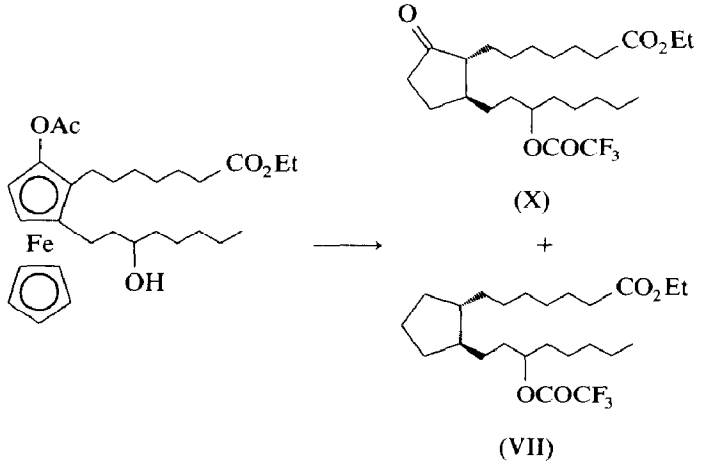


All natural prostaglandins have the allyl alcohol entity contained within a C_8 chain and an oxygen function, a hydroxyl or ketone group, in the cyclopentane ring [11]. We were interested in finding out whether the hydrogenolysis could be carried out with retention of a wide range of functional groups. It is, of course, impossible to keep the double bond during the hydrogenolysis. Under the usual conditions, in CF_3COOH solution, it is also impossible to retain hydroxyl at C-15 because of the stability of α-ferrocenylcarbenium ion, that is formed by the migration of a double bond. As a result the hydrogenation was carried out initially with Pd/C in *ethanol* at 20 °C. Subsequently the di- and tri- substituted ferrocene analogues of prostaglandins were hydrogenated under standard conditions [12].

It should be noted that complete trifluoroacetylation of the hydroxyl group at C-15 takes place during hydrogenolysis, and is probably accompanied by complete randomization at this chiral centre. No optical activity was observed in the products. The ^{13}C NMR spectra indicate that two diastereomers with the *trans*-arrangement of hydrocarbon chains (major products) and two with the *cis*-arrangement (minor products) are formed; thus the diastereoselectivity is the same as in the case of prostanoic acid.



In the hydrogenolysis of a trisubstituted compound, the main question concerned the behaviour of the acetoxy group attached to ferrocene. One of the two products appeared to be the disubstituted compound VII, previously obtained. The other one was shown to be the cyclopentanone derivative X (*trans*-isomer), which is probably formed by the hydrolysis of its precursor, acetoxyenole, which is the primary product of the hydrogenolysis.

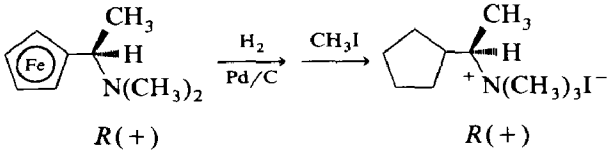


Taking into account the preceding steps, this hydrogenolysis completes the synthesis of 9,11-bis-deoxy-13,14-dihydro-15-*O*-trifluoroacetyl-PGF_1 in 9 steps and of 11-deoxy-13,14-dihydro-15-*O*-trifluoroacetyl-PGE_1 in 12 steps, starting from ferrocene itself. In summary, the ferrocene route permits the preparation of prostanoids in racemic form but with a desired stereoselectivity.

Retention of optical activity due to a chiral centre in a side chain

As was shown above, optical activity due to planar chirality of the ferrocene system is lost completely under the conditions of hydrogenolysis. It was of interest to find an example whose optical activity would persist in this procedure. A

ferrocene compound with a chiral centre at α-carbon was chosen. It is now known that oxygen functions at the α-carbon do not resist hydrogenolysis. However, it is possible to obtain an optically active product from the hydrogenolysis of α-(*N*,*N*-dimethylamino)ethylferrocene. Optically active α-(*N*,*N*-dimethylamino)ethylcyclopentane was isolated as a quaternary salt in low yield. The hydrogenolysis of the carbon–nitrogen bond is probably a concomitant process, but no attempt has yet been made to alter the standard conditions. Since all the bonds around the chiral centre were not affected during the hydrogenation the absolute configuration of the cyclopentane was assigned as shown.



R(+) *R*(+)

We hope soon to study the behaviour of compounds containing both a chiral centre and a chiral plane.

Experimental

Standard conditions for the hydrogenolysis experiments (unless otherwise stated) were as follows: Pd/C catalyst in pure CF_3COOH at 50 °C and 1 atm of H_2. The catalyst, 10% Pd/C, was prepared by a published procedure [13] using charcoal "Darco G-60", Serva. The NMR spectra were recorded on a Bruker WN-200 instrument, CF_3COOH was used as the external standard for the ^{19}F NMR spectra. Optical rotations were determined using a Perkin–Elmer 241 polarimeter.

Hydrogenolysis of 1-(6-carboxyhexyl)-2-octylferrocene as ethyl ester:

(i) in CF_3COOH

To a solution of 0,4017 g (0.87 m*M*) of the title compound ($[\alpha]_{578}$ +0.35°, e.e. 55%) in CF_3COOH (20 ml) was added 0.8 g of Pd/C and H_2 was bubbled through for 4 h. The catalyst was then filtered off, the solution was evaporated to dryness, and the residue was dried over KOH in vacuo. The product was treated with water and ether from which was isolated 0.2279 g (78%) of 1-(6-carboxyhexyl)-2-octylcyclopentane as ethyl ester. IR: ν 1735 cm^{-1} (COOEt). ^1H NMR (C_6D_6), δ (ppm): 0.92 (t, CH_3, ω-chain), 0.99 (t, CH_3CH_2OCO), 1.18–1.70 (m, CH_2), 1.82 (m, CH), 2.16 (t, CH_2COOEt), 3.98 (q, CH_3CH_2OCO). ^{13}C NMR (C_6D_6), δ: 14.11 and 14.25 (CH_3), 22.67 and 30.45 (ring CH_2 of *cis*-isomer), 23.99 and 35.50 (ring CH_2 of *trans*-isomer), 28.58 and 28.78 (CH_2 adjacent to ring, *cis*-isomer), 32.48 and 34.58 (CH_2 adjacent to ring, *trans*-isomer), 22.78, 25.14, 28.45, 28.67, 29.29, 29.46, 29.79 (the rest of CH_2 groups), 42.74 (CH of *cis*-isomer), 46.11 and 46.15 (CH of *trans*-isomer).

(ii) in $CH_3COOH + HClO_4$

To a solution of 0.4115 g (0,91 m*M*) of the same compound in acetic acid (20 ml) was added 0.8 g of Pd/C and 2 ml of 72% aqueous $HClO_4$, then H_2 was bubbled through for 8 h at 50 °C. The catalyst was filtered off, and the residue was diluted

with water and ether. The ethereal extract was concentrated and chromatographed on the Silufol plates with benzene as eluant. Two products were isolated: 0.040 g (13%) of the ester mentioned above and 0.068 g (25%) of the parent acid.

Ethyl ester of 1-(6-carboxyhexyl)-2-(3'-hydroxyoctyl)ferrocene, VI. To 0.5238 g (1.12 m*M*) of ethyl ester of 1-(6-carboxyhexyl)-2-(3-hydroxy-oct-1-enyl)ferrocene in ethanol (30 ml) was added 0.6 g of Pd/C, and H_2 was bubbled through at 20 °C for 2.5 hrs. After filtration the solution was concentrated and chromatographed on a SiO_2 column with benzene-ether (5 : 1) as eluent. The yield of the product VI was 0.4029 g (77%). Found: C, 69.25; H, 8.41. $C_{27}H_{42}FeO_3$ calc: C, 68.91; H, 9.00%. IR ν (cm^{-1}): 1741 (COOEt), 3105 (C_5H_n) 3300–3600 (OH). ^1H NMR (C_6D_6), δ (ppm): 0.91 (t, CH_3 of ω-chain), 0.98 (t, CH_3CH_2OCO), 1.15–1.75 (CH_2 groups), 2.15 (q, CH_2COOR), 2.32 (m, α-CH_2 of α-chain), 2.38–2.70 (m, α-CH_2 of ω-chain), 3.48–3.59 (m, CHOH), 4.01 (s, C_5H_5), 3.92–4.05 (CH_3CH_2OCO and C_5H_3).

Ethyl ester of 1-(6-carboxyhexyl)-2-(3'-trifluoroacetoxyoctyl)cyclopentane, VII + VIII. 0.2323 g (0.49 m*M*) of VI was hydrogenated in CF_3COOH (20 ml) with 0.25 g of Pd/C for 4 h. After the usual work-up the residue was chromatographed on Silufol with hexane-ether (30 : 1) to afford 0.1510 g (68%) of VII and VIII. Found: C, 64.18; H, 9.33; F, 12.42. $C_{24}H_{41}F_3O_4$ calc: C, 63.97; H, 9.17; F, 12.65%. IR, ν (cm^{-1}): 1750 (COOEt), 1786 ($OCOCF_3$). ^1H NMR (C_6D_6): 0.83 (t, CH_3 of ω-chain), 0.97 (t, CH_3CH_2OCO), 1.00–1.72 (CH_2 groups), 2.14 (t, CH_2COOEt), 3.96 (q, CH_3CH_2OCO), 4.9 (m, $CHOCOCF_3$). ^{19}F NMR (C_6H_6), δ (ppm): −3.11 (s) and −3.13 (s), 2 diastereomers. ^{13}C NMR (C_6D_6), δ (ppm): 13.92 (C-20), 14.27 (CH_3CH_2O), 42.12, 42.28, 43.34, 43.57 (C-8 and C-12, *cis*-isomers, 2 diastereomers), 45.49, 45.70, 45.88, 45.92 (C-8 and C-12, *trans*-isomers, 2 diastereomers), 60.21 (CH_3CH_2O), 80.07, 80.42 (C-15, 2 diastereomers), 114.73 (q,$OCOCF_3$) 157.41 (q, $OCOCF_3$), 174.02 (COOR), the rest of the CH_2 groups are in the interval 22.4–36.2.

Ethyl ester of 1-acetoxy-2-(6-carboxyhexyl)-3-(3'-hydroxyoctyl)ferrocene, IX. 0.400 g (0.76 m*M*) of the ethyl ester of 1-acetoxy-2-(6-carboxyhexyl)-3-(3'-hydroxyoct-1'-enyl)ferrocene was hydrogenated in ethanol (30 ml) with 0.4 g of Pd/C for 2.5 h at 20 °C. After the usual work-up two products were separated by chromatography on Silufol (hexane-ether 2 : 1). 0.074 g (18%) of VI and 0.233 g (58%) of IX were obtained. Found: C, 66.93; H, 8.72. $C_{29}H_{44}FeO_5$ (IX) calc: C, 65.88; H, 8.39%.

Hydrogenolysis of IX. Synthesis of ethyl ester of 2-(6-carboxy-3-(3'-trifluoroacetoxy-octyl)cyclopentanone-1, X. 0.1562 g (0.30 m*M*) of IX was hydrogenated with 0.2 g of Pd/C in 15 ml of CF_3COOH for 5 h. After the usual work-up the dry residue was extracted with pentane from which a crude mixture of VII and X was obtained. It was separated by chromatography on Silufol with benzene as eluent to give 0.0283 g (22%) of the previously known VII and 0.0281 g (21%) of a new compound X. Found: C, 62.82; H, 8.90. $C_{24}H_{39}F_3O_5$ (X) calc: C, 62.05; H, 8,46%. IR, ν (cm^{-1}): 1750 (COOEt and CO), 1795 ($OCOCF_3$). ^1H NMR (C_6D_6), δ: 4.9 (m, $CHOCOCF_3$). ^{19}F NMR, δ: −2.45 and −2.50 (2 diastereomers). ^{13}C NMR, δ: 13.76 (C-20), 37.62 (C-10), 40.98 and 41.26 (C-12, 2 diastereomers), 54.73 (C-8), 79.45 and 79.77 (C-15, 2 diastereomers), 173.9 (COOR), 218.7 (C=O).

Hydrogenolysis of (+)-N,N-dimethylaminoethylferrocene. 0.3 g (1.17 m*M*) of *α-N,N*,dimethylaminoethylferrocene ($[\alpha]_D$ +10.4° c 3,9, EtOH, e.e. 73%) was hydrogenated with 0.6 g of Pd/C in 30 ml of CF_3COOH at 50 °C for 1.5 h. After filtration, solvent was evaporated, the residue was diluted with water, neutralized with Na_2CO_3 and extracted with ether. The ethereal solution was dried over K_2CO_3,

the ether was removed, the residue was extracted with acetone and treated with methyl iodide. After 1 h the addition of ether afforded 0.011 g (3.3%) of *N,N,N*,-trimethyl-(1-cyclopentyl)ethylammonium iodide, $[\alpha]_D$ +9.1° (c 0,44, EtOH). ^{1}H NMR ($CDCl_3$), δ: 1.41 (d, CH_3CH), 1.5–2.3 (CH_2 groups), 2.6 (m, ring C*H*), 3.42 (s, CH_3N), 4.03 (m, C*H*–N).

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