ASYMMETRIC CYCLOPALLADATION IN THE FERROCENE SERIES AS A TOOL FOR ENANTIOSELECTIVE SYNTHESIS. PREPARATION OF SOME ANALOGUES OF NATURAL PRODUCTS

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Summary

The previously described asymmetric cyclopalladation has been applied to the esters of 7-dimethylamino-7-ferrocenylenanthic acid, I, to afford the optically active palladium derivative, II. The absolute configuration of the chiral plane is determined by the configuration of the inductor: the acylamino acid salt. The palladium atom in II was then substituted by a σ-ketovinyl group using the reaction with pentyl vinyl ketone, to yield III. The latter substance undergoes full reduction when treated with $Et_3SiH + CF_3COOH$ (the ionic hydrogenation reaction) resulting in the optically active prostanoic acid analogue, IV. On the other hand, III in the form of the methiodide is reduced by $NaBH_4$ with the elimination of the amine group and the formation of allyl alcohol V. This kind of side chain is characteristic of many prostaglandins. Bromination of II followed by the repeated cyclopalladation opens the way to trisubstituted derivatives. The pathway outlined provides a rapid synthesis of optically active compounds which are the ferrocene analogues of natural prostaglandins .

Introduction

The high reactivity of organopalladium compounds containing both σ- and π-bonded organic ligands has been used widely in organic synthesis [1,2]. The introduction of organopalladium reagents made it possible to accomplish a number of reactions by means of which certain functional groups are inserted into the molecule in a regioselective and stereoselective way. Up to now, however, this method has found almost no application in enantioselective synthesis. This is quite understandable since the known optically active organopalladiums are very few and difficult to obtain with a high degree of enantiomeric purity. As fas as we know, the first optically active σ-organopalladium derivative was described about a decade ago [3]. Both chemical and configurational stability of that molecule were ensured by the

incorporation of the chiral carbon into chelated metallocycle. A more useful method for the preparation of the same compound as enantiomers was published very recently [4].
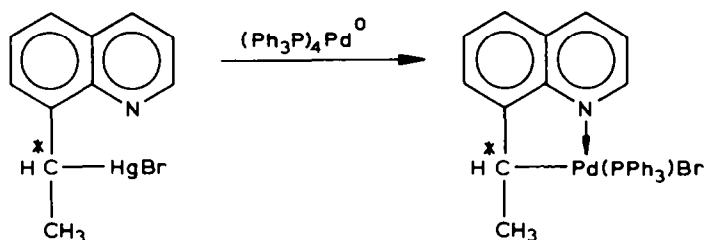
Enantiomeric organopalladiums with open chain and benzylic chiral centre are also known [5]. Optically active organopalladiums of the π-allyl type containing a non-symmetrically substituted ligand should have planar chirality. Enantiomers of such a type are unknown but several diastereomeric Pd-allyl complexes in the terpenoid and steroid series have been obtained [6,7].

Optically active palladium derivatives with planar chirality in the ferrocene series

Planar chirality is known to occur in the metallocenes derivatives. Recently, we found a preparative method for the asymmetric cyclopalladation of dimethyl-aminomethylferrocene which makes it possible to obtain the enantiomeric organo-palladium, R = H in optical yield of up to 80–90% [8,9]. Cyclopalladation of chiral aminoalkyl ferrocenes results in both asymmetric induction of planar chirality and partial resolution at the chiral centre.
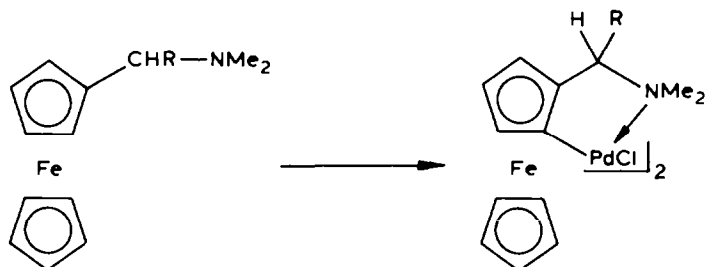

The C–Pd bond has normal reactivity and undergoes readily the usual reactions with carbon monoxide and alkylvinylketones [10,11]. It is important to note that after the palladium atom is substituted by some other group the dimethylamino group released is capable of promoting repeated cyclopalladation into the second neighbour position in the ferrocene ring. The cyclopalladation reaction thus offers a possibility to arrive at enantiomeric di-, tri- and even tetra-substituted homoannular ferrocenes.

The highly effective asymmetric synthesis of reactive organopalladium ferrocenes suggested to us that it might be possible to synthesize in a rather simple way the analogues of some natural compounds avoiding the difficult stage of resolving racemates into enantiomers.

Retrosynthetic analysis

The ferrocene molecule like all cyclopentadienyl complexes is based on the

five-membered carbocycle. At least two methods are known in the literature for the decomplexation of a C_5 ring, arriving in the end at cyclopentane derivatives, possibly via dehydroderivatives [12,13]. Therefore, ferrocenes can be regarded as the structural precursors of cyclopentanes. Owing to the nature of ferrocene chemistry some side chains can be constructed in a simpler way than for cyclopentane. It should be noted that the planar chirality in disubstituted homoannular ferrocenes will be replaced by the central chirality (two chiral centres) in the resulting cyclopentanes, which allows the possibility of the stereo-selective enantiomer-to-enantiomer transition as shown below.
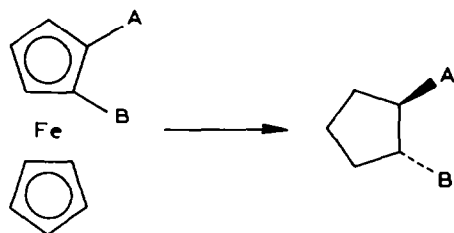
Among the natural cyclopentane molecules a special place is occupied by compounds of a strong and diverse biological activity known as the class of prostaglandins, whose characteristic structural features are represented by the formula:
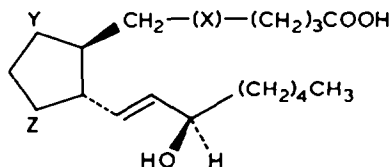
$(X = CH_2CH_2$ or $cis-HC{=}CH)$

The two long side chains occupy neighbouring positions in the cycle. The allyl alcohol unit can be obtained from vinyl ketone which is easily accessible from the Pd derivative [11]. Asymmetric cyclopalladation must ensure the optical activity in the ferrocane analogue due to the planar chirality. The third substituent can be introduced using repeated cyclopalladation of the simple, non-asymmetric variant. The ferrocene analogues of prostaglandins are interesting not only as intermediates for their synthesis but they themselves can exhibit physiological activity, since ferrocene metabolism seems to occur by means of decomplexation, which is probably why they can serve as precursors of prostaglandins in vivo. Moreover, the recent study on the synthesis and properties of prostaglandin analogues based on a benzene instead of a cyclopentane nucleus showed that one of the compounds exhibited considerable activity [14].

The strategical principles outlined above allow some variety of tactical solutions. The key step is invariably the asymmetric cyclopalladation, possibly repeated, followed by the modification of the side chains which is facilitated by the specific effect of the ferrocene group. The following transition to purely organic compounds by removal of the cyclopentadienyliron group can be predicted. In connection with this plan, of special interest among the numerous approaches to racemic prostaglandins is the brilliant synthesis by Holton [15] who used twice the regio- and

stereo-selective but not enantioselective cyclopalladation, although of the double bond and not of the aromatic system.

Results and discussion

Synthesis of the enantiomeric analogue of prostanoic acid

The parent molecule of the prostaglandin class is prostanoic acid whose molecule has only two long chains in *trans*-positions with no functional groups except the terminal carboxyl; oxygen functions in positions 9 and 11 being absent *. Its ferrocene analogue was chosen as the first goal.

We have chose a route (see Scheme 1) according to which the shorter chain with the terminal ester group is introduced in the ferrocene ring from the very beginning. This chain also contains a keto group α to ferrocenyl which may be easily converted to a dimethylamino group [21]; the relevant experiments were reported previously [16]. The dimethylamino group plays an important role directing asymmetric cyclopalladation and is removed later.


SCHEME 1

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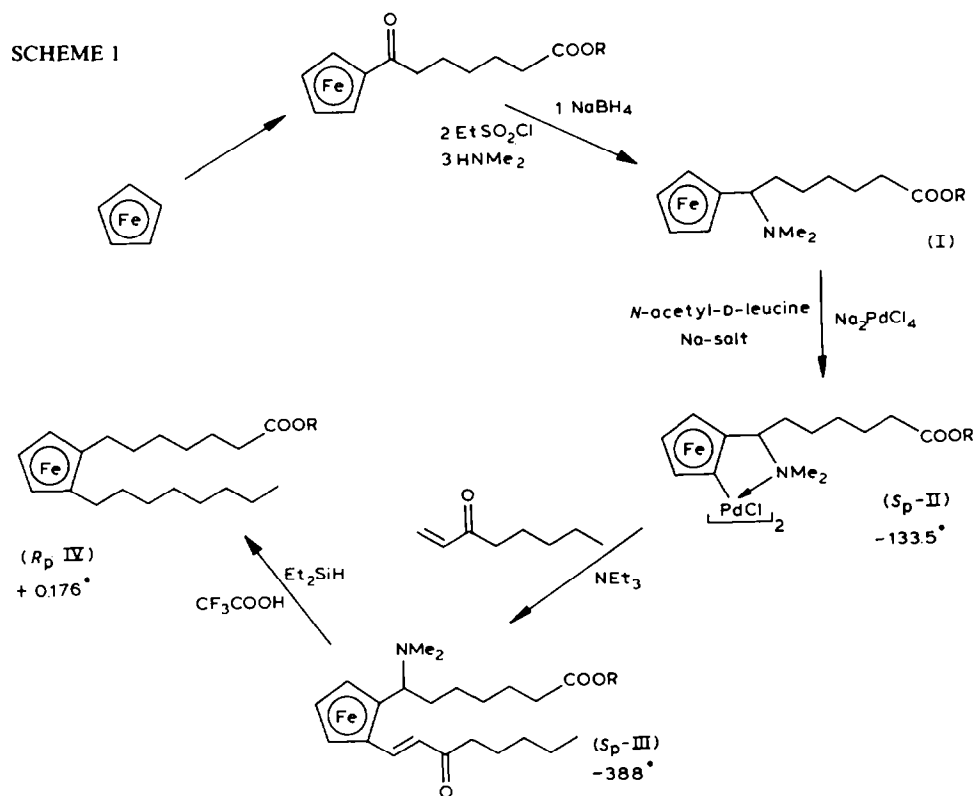
* The conventional numeration of carbon atoms in prostaglandins is as shown here:
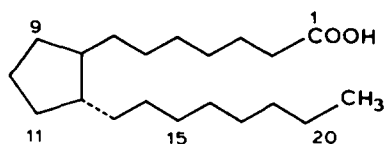
In ferrocene-Pd derivatives the sign of optical rotation is known to be determined by the absolute configuration of the chiral plane [17]. Therefore, one can assign at once the absolute configuration for all the molecules in the Scheme including the analogue of prostanoic acid, IV, whose low optical rotation is quite understandable since the structural difference between two long chains is very small (COOR vs. C_2H_5).

Ketovinylation of Pd metallocycles has been described by several authors [10,11,18,19]. We have observed that in the course of this reaction in the absence of triethylamine the formation of the normal product III is accompanied by the partial elimination of the Me_2N group to give compound V with an additional double bond. The mixture can be separated by preparative thin-layer chromatography.
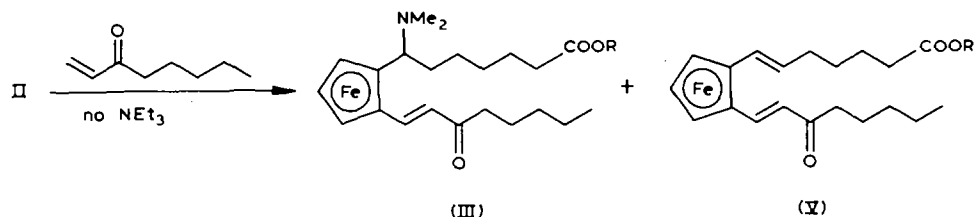
Very unusual is the replacement of Me_2N by H during the reduction of III with Et_3SiH and CF_3COOH (so-called "Ionic Hydrogenation") which has not been observed before [20]. The development of a substantial positive charge on the α-carbon due to protonation of nitrogen is probably responsible for such abnormal behaviour.

Synthesis of optically active ferrocenes containing functional groups characteristic of prostaglandins

The Et_3SiH–CF_3COOH reduction appeared to be a severe method that removed any unsaturation in side carbon chains. Milder treatment with $NaBH_4$ in aqueous ethanol yielded the allylic alcohol moiety. If the dimethylamino group was previously quaternised it is simultaneously replaced by a hydrogen atom. Due to the formation of a new chiral centre at C(15), two diastereomers are formed in unequal quantities *. In this way it is possible to build in the molecule the characteristic allylic alcohol fragment as in VI.
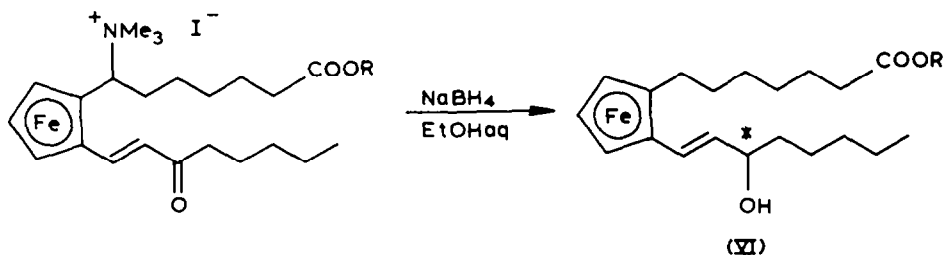

As a precursor of the oxygen function in the ferrocene ring we used bromine, since it was known that a halogen atom can be exchanged for acetoxyl [22].

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* Similarly, all di- and tri-substituted ferrocenes with a chiral centre at C(7) or C(15) are mixtures of diastereomers.

Bromination of enantiomeric II afforded the desired bromide VII in fair yield (Scheme 2). Repeated cyclopalladation with $NaOCOCH_3$ as catalyst gave a trisubstituted organopalladium VIII which was then treated with pentyl vinyl ketone to yield IX. The latter reaction is shown by PMR spectroscopy and elemental analysis to be accompanied by partial debromination, a mixture of di- and tri-substituted ferrocenes being formed in an approximate ratio IX : III = 1 : 2. The second cyclopalladation can be also performed with ferrocenole acetate X. Finally, the application of borohydride reduction of the quaternary ammonium salt as described above is thought to result in the synthesis of the ferrocene analogue of the prostaglandin 11-desoxy-PGF₁.

SCHEME 2
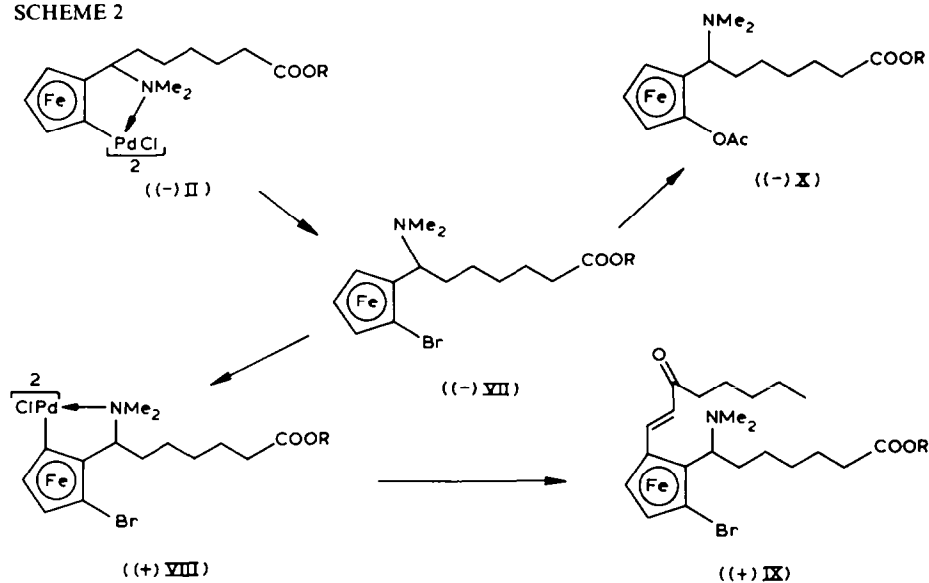
Experimental

Methods and instruments were those used previously [9]. All optical rotations were taken at 578 nm. All experiments were performed under argon. The ethyl ester of 7-oxo-7-ferrocenylenanthic acid was prepared by Friedel-Crafts acylation. Subsequent reduction with $NaBH_4$ in aqueous ethanol gave the corresponding 7-hydroxy derivative [16].

Ethyl ester of 7-dimethylamino-7-ferrocenylenanthic acid, I

A solution of 13.4 g of $C_2H_5SO_2Cl$ in 10 ml of CH_2Cl_2 was added upon stirring to a solution of the above carbinol (12.2 g) and trimethylamine (10.0 g) in CH_2Cl_2 (60 ml) at −78°C. After 3 h, 13.4 g of dimethylamine in 40 ml of isopropanol were slowly added, the mixture was allowed to reach room temperature and was left overnight. Then solvents were evaporated off, and the residue was dissolved in CH_2Cl_2 and hexane. The solution was extracted three times with 40% H_3PO_4 and then with water. The combined extract was washed with ether, adjusted to pH 8–9

with Na_2CO_3 and the product was isolated with ether. The oily I weighted 12.8 g (98%). ^{1}H NMR: δ 1.88 -NMe_2 (CCl_4) Anal. found: C, 65.89; H, 8.41. calcd. for $C_{21}H_{31}FeNO_2$: C, 65.46; H, 8.11%.

Di-μ-chlorobis-(1'-dimethylamino-6'-carbethoxyhexyl)(1'C,1'N-)-dipalladium, II

A solution of 5.1 g of the Na salt of N-acetyl-D-leucine and 1.2 g NaOH in 40 ml of water were added to a solution of 8.65 g of Na_2PdCl_4 in 120 ml of MeOH, and the obtained solution was brought to pH 7.35 by adding a small amount of conc. aqueous NaOH. A solution of 11.3 g of amine I in 40 ml of MeOH was then added, and the mixture left overnight. On the next day methanol was removed in vacuo. Extraction with benzene afforded 15.3 g (98.5%) of palladium dimer II as an oil which was transformed into a solid by triturating with pentane; the yield of pure II is 70%, $[\alpha]$ $-$ 133.5° (CH_2Cl_2, c 2.1). In a similar way racemic II was prepared in the presence of sodium acetate. Anal., found: C, 47.95; H, 5.61; Cl, 6.95; N, 2.66. Calcd. for $C_{21}H_{30}ClFeNO_2Pd$: C, 48.28; H, 5.64; Cl, 7.08; N, 2.84%.

1-(Octenyl-1'-on-3')-2-(6'-carbethoxy-1'-dimethylaminohexyl)ferrocene, III

A. 1.5 g of pentylvinyl ketone and 1.5 g of triethylamine were added to a solution of 5.3 g of dimer II in 200 ml of toluene, and the mixture was refluxed for 5 h. After filtration and the removal of solvent in vacuo the crude product was chromatographed on silica gel (hexane–triethylamine, 6 : 1). The yield or pure III was 3.1 g (61%), oil, $[\alpha] - 388°$ (EtOH, c 1.1). Anal., found: C, 68.69; H, 8.43, Calcd. for $C_{29}H_{43}FeNO_3$: C, 68.41; H, 8.43%.

B. *With no* Et_3N *added.* A solution of 7.3 g of ($-$)II and of 2.1 g of pentylvinyl ketone in 250 ml of toluene was refluxed for 5 hrs. Then 20 ml of triethylamine were added and the residue after the evaporation of solvent (3.5 g) was chromatographed on Silufol. Fraction 1 (0.7 g, 10%): 1-(Oct-1'-en-3'-on)-2-(6'-carbethoxyhex-1'-enyl)ferrocene, V, $[\alpha] - 184°$ (EtOH, c 0.85). Anal., found: C, 69.81; H, 7.71. Calcd. for $C_{27}H_{36}FeO_3$: C, 69.83; H, 7.96%. Fraction 2 (0.7 g, 10%): identical to III in the previous experiment A.

1-(6'-Carbethoxyhexyl)-2-octylferrocene, IV

The analogue of prostanoic acid, IV, was obtained by the conventional procedure of ionic hydrogenation from ketovinylamine III and triethylsilane in CF_3COOH at room temperature; yield 67%, oil, after chromatography $[\alpha] + 0.176°$ (EtOH, c 11.3). Anal., found: C, 71.22; H, 9.31. Calcd. for $C_{27}H_{42}FeO_2$: C, 71.35; H, 9.32%.

1-(6'-Carbethoxyhexyl)-2-(octenyl-1'-ol-3')ferrocene, VI

A solution of 3.0 g of amine III in 50 ml of acetone was treated at $-5°C$ with 1 ml of methyl iodide, and after 30 min the methiodide was isolated with pentane. The dried solid was dissolved in ethanol (50 ml), 1 g of $NaBH_4$ in 10 ml of water was added and the mixture was stirred for 1 h, and then extracted with ether. The crude product was chromatographed on silica gel (eluent ether/benzene, 1/5) to afford 0.4 g (36.5%) of oily VI. IR: 3400 (OH), 1660 (C=C), 1730 (C=O) cm^{-1}. Anal. found: C, 68.57; H, 8.78. Calcd.: C, 69.27; H, 8.54%. $[\alpha] - 114.5°$ (EtOH, c 2.6).

2-Bromo-1-(1'-dimethylamino-6'-carbethoxyhexyl)ferrocene, VII

0.53 g of dimer II was dissolved at room temperature in 30 ml of CH_2Cl_2 and

0.05 ml of bromine in 10 ml of CH_2Cl_2 was added dropwise. After stirring for 30 min the solvent was removed in vacuo and residue was chromatographed on silica gel, eluting first with benzene and then bromoamine VII was obtained with hexane–triethylamine, (5:1). The yield of the product (mixture of two diastereomers, according to PMR spectrum) was 0.20 g (43%), $[\alpha] - 4.05°$ (EtOH, c 3.8). An analytical sample was obtained after repeated chromatography, found: C, 54.49; H, 6.59; Br, 17.13. Calcd. for $C_{21}H_{30}BrFeNO_2$: C, 54.33; H, 6.51; Br, 17.21%.

Cyclopalladation of (−)VII was performed according to the conventional procedure [9], starting from 24.0 g of VII, 15.1 g of Na_2PdCl_4 and 7.2 g of $CH_3COONa \cdot 3H_2O$. After usual work-up 24.0 g of product VIII (76.9%) was obtained, $[\alpha] + 129°$ (CH_2Cl_2, c 6.7).

Acknowledgement

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* This sample of VII had optical rotation $[\alpha] - 4.7°$.