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SYNTHESIS OF 3-FERROCENYL-3,3a,4,5-TETRAHYDRO-2*H*-BENZO[*g*]INDAZOLES

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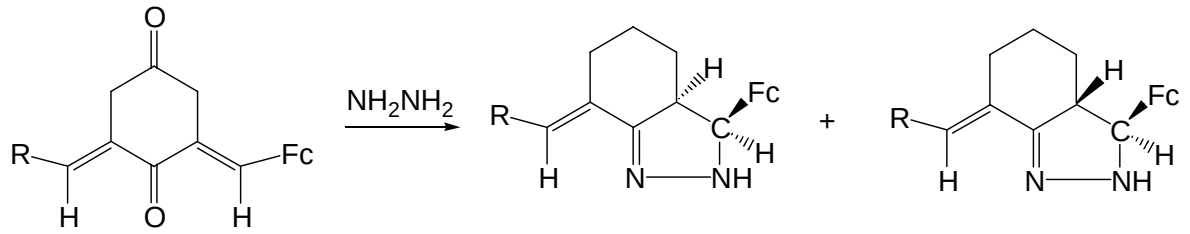
Abstract – The reactions of *E*-2-ferrocenylmethylidenetetralones with hydrazine proceed diastereoselectively, forming the *cis* isomers of diazatricycles in high yields. The studies of the anti-inflammatory activity of *E*-2-ferrocenylmethylidenetetralones and *N*-acetylindazoles showed a moderate activity in a TPA model. The structure of 2-acetyl-3-ferrocenyl-6-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole was confirmed by X-Ray diffraction analysis.

INTRODUCTION

It is known that nine types of asymmetrical induction can occur in molecules of organic compounds depending on the nature of their chiral elements, namely: center-center, center-axis, center-plane, axis-center, axis-axis, axis-plane, plane-center, plane-axis, plane-plane.[1] Due to characteristic steric features of the metallocene system of ferrocene, the ferrocenyl substituent in a molecule of an organic compound can induce the following types of asymmetry: chiral plane-chiral center, chiral center-chiral plane, and chiral center-chiral center.[1-4] When prochiral starting compounds are used, this effect leads to the formation of a mixture of diastereomers with different ratios or of only one of them.

The stereochemical aspects of the synthesis of heterocyclic systems on the basis of prochiral α,β-enones with a ferrocene fragment in the molecule have been studied on a limited number of examples. High diastereoselectivity of formation of 2-pirazolines from α,β-enones bearing ferrocenyl and phenyl-butadienyltricarbonyl iron substituents in positions 3 and 5 of the pyrazoline ring was explained by asymmetrical induction of the chiral center by the chiral plane or *vice versa* of the 1,3 and 1,1 type.[5] High diastereoselectivity was also observed in the synthesis of bicyclic and policyclic ferrocenyl-4,5-dihydropyrazoles based on *E,E*-bis(ferrocenylmethylidene)cycloalkanones[6,7] and *E*- or *Z-s-cis*- and *s-trans*-α,β-ferrocenylenones[8,9] (Scheme 1).



R= Fc; Fc=$C_5H_5FeC_5H_4$

Cis (a)

60- 80 %

Trans (b)

20- 40 %

Scheme 1. Formation of chiral centers

The preferential formation of the five-membered heterocycles with *cis*-orientation of hydrogen atoms (**a**) was observed.[6,7]

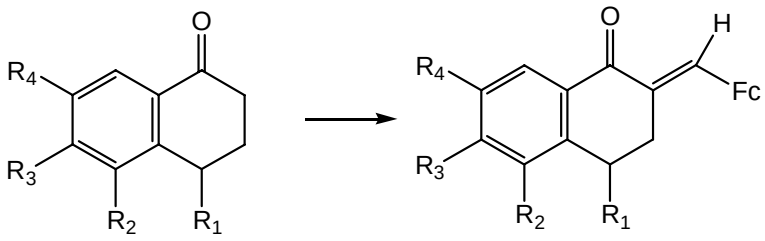
The interest in diastereoselective synthesis is currently associated with pharmacological demands for the production of new drugs. It has been established that compounds having ferrocenyl substituents manifest biological activity. For example, ferrocenyl-substituted dihydropyrazoles, cyclopropanes, cyclohexenes, tetrahydrophthalates, alkylazoles have anti-inflammatory,[10-12] analgesic,[12,13] antiviral[10] and anti-malignanty[14] activities. Different diastereomeric forms of the same compound could possess different biological activities.

Therefore, it is interesting to study the ability of a ferrocene substituent to induce diastereoselectivity and to test their biological activity. In the present paper we report on the diastereoselectivity in the synthesis of tricyclic ferrocenyldihydropyrazoles (**19-24**) from 2-ferrocenylmethylidene-1-tetralones (**7-12**) and the biological activity of both type of compounds, tetralones (**7-12**) and corresponding dihydropyrazoles (**19-24**).

RESULTS AND DISCUSSION

α,β-Enones (**7-12**) served as the starting compounds. They were prepared by condensation of ferrocene-carboxyaldehyde with the corresponding α-tetralones (**1-6**) in presence of NaOH in aqueous ethanol at

room temperature[7] (Scheme 2):



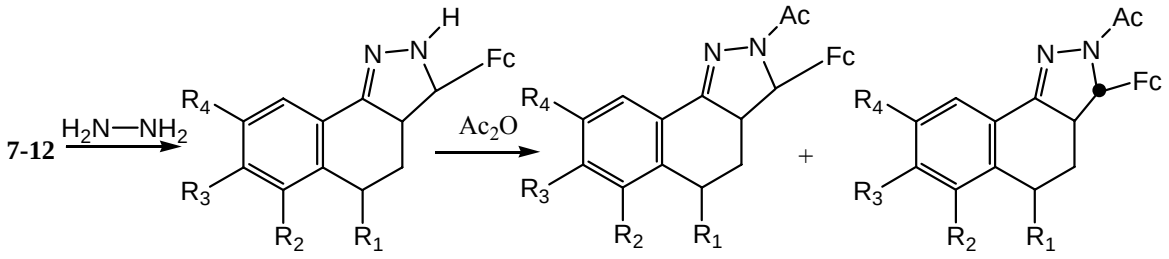
1-6 **7-12**

(1,7) $R_1=R_3=R_4=H$, $R_2=OCH_3$
(2,8) $R_1=R_2=R_4=H$, $R_3=OCH_3$
(3,9) $R_1=R_2=R_3=H$, $R_4=OCH_3$
(4,10) $R_1=R_3=H$, $R_2=R_4=OCH_3$
(5,11) $R_2=R_3=R_4=H$, $R_1=CH_3$
(6,12) $R_1=R_2=R_3=R_4=H$
$Fc=C_5H_5FeC_5H_4$

Scheme 2. Synthesis of α,β-enones

Enones (**7-12**) were formed as single *E*-geometrical isomers with an 'outward' arrangement of the bulky ferrocenyl substituents in respect to the *s-cis*-heterodiene systems.[6,15] The ^1H and ^{13}C NMR spectroscopic data for compounds (**7-12**) are listed in Tables 1 and 2.

1-Acetyl-4,5-dihydropyrazoles (**19-24**) (Scheme 3) were obtained from enones (**7-12**) by addition of hydrazine[16,17] followed by the acetylation of the relatively unstable nitrogen intermediates (**13-18**). These compounds (**13-18**) are stable in dry state but rapidly decompose in solutions, fact that precludes their characterization by ^1H NMR spectroscopy. The data obtained from the elemental analyses of compounds (**13-18**) are listed in Table 3.



13-18 **19a-24a** **19b,22b-24b**

(13, 19a,b) $R_1=R_3=R_4=H$, $R_2=OCH_3$
(14, 20a) $R_1=R_2=R_4=H$, $R_3=OCH_3$
(15, 21a) $R_1=R_2=R_3=H$, $R_4=OCH_3$
(16, 22a,b) $R_1=R_3=H$, $R_2=R_4=CH_3$
(17, 23a,b) $R_2=R_3=R_4=H$, $R_1=CH_3$
(**18, 24a,b**) $R_1=R_2=R_3=R_4=H$

Scheme 3. Synthesis of 1-acetyl-4,5-dihydropyrazoles (**19-24**)

We found that pyrazolines (**19, 22-24**) were formed as mixtures of two diastereomeric forms in different ratios. These forms differ in their physical parameters and are characterized by similar ^1H and ^{13}C NMR

spectra (Tables 1 and 2). The diastereomeric form, which is present in a larger amount in all the cases, is denoted as *cis* isomer (**a**) and the minor diastereomeric form is denoted as *trans* isomer (**b**). *N*-Acetyl-dihydropyrazoles (**20** and **21**) were formed as a single diastereomeric form of **a**.

Table 1. ^{1}H NMR spectral data of compounds (**19a-24a**, **19b, 22b-24b** and **7-12**) (δ, *J*/Hz)

Compound	C_5H_5, s	C_5H_4, m	CH, CH_3	CH_2	Ar
7	4.17 (5H)	4.44 (2H), 4.57 (2H)	3.88 s (3H), 7.67 s (1H)	2.94 bs (4H)	7.03 dd (1H), *J* = 1.1, 8.1; 7.31 t (1H), *J* = 8.1; 7.41 dd (1H), *J* = 1.1, 8.1
8	4.17 (5H)	4.43 (2H), 4.55 (2H)	3.87 s (3H), 7.65 s (1H)	2.95 dm (4H), *J* = 5.71	6.71 d (1H), *J* = 2.3; 6.85 dd (1H), *J* = 2.3, 8.7; 8.09 d (1H), *J* = 8.7
9	4.18 (5H)	4.45 (2H), 4.57 (2H)	3.87 s (3H), 7.69 s (1H)	2.89 m (2H), 2.96 m (2H)	7.05 dd (1H), *J* = 3.0, 8.4; 7.16 d (1H), *J* = 8.4; 7.61 d (1H), *J* = 3.0
10	4.17 (5H)	4.44 (2H), 4.56 (2H)	2.31 s (3H), 2.36 s (3H), 7.64 s (1H)	2.84 m (2H), 2.96 m (2H)	7.19 bs (1H), 7.81 d (1H), *J* = 0.6
11	4.18 (5H)	4.45 (2H), 4.57 (1H), 4.61 (1H)	1.32 d (3H), *J* = 6.2; 3.14 m (1H), *J* = 6.2; 7.76 (1H)	2.95 m (4H)	7.33 m (2H), 7.51 td (1H), *J* = 1.5, 7.7; 8.11 dd (1H), *J* = 1.5, 7.7
12	4.17 (5H)	4.44 (2H), 4.56 (2H)	7.70 s (1H)	2.97 m (4H)	7.24 dd (1H), *J* = 0.75, 7.8; 7.35 td (1H), *J* =1.2, 7.8; 7.47 td (1H), *J* = 0.75, 7.5; 8.11 dd (1H), *J* = 1.2, 7.5
19a	4.15 (5H)	4.10 (1H), 4.17 (1H), 4.19 (1H), 4.45 (1H)	2.31 s (3H), 3.67 m (1H), 3.88 s (3H), 4.93 d (1H), *J* = 6.92	1.99 m (1H), 2.47 m (1H), 2.81 m (1H), 3.16 m (1H)	6.9 dd (1H), *J* = 0.9, 7.8; 7.29 t (1H), *J* = 7.8; 7.55 dd (1H), *J* = 0.9, 7.8
19b	4.23 (5H)	4.02 (1H), 4.12 (1H), 4.15 (1H), 4.17 (1H)	2.47 s (3H), 3.79 s (3H), 3.84 m (1H), 5.62 d (1H), *J* = 9.31	1.83 m (1H), 2.38 m (1H), 3.08 m (1H), 3.28 (1H)	6.87 dd (1H), *J* = 0.9, 8.1; 7.21 m (1H), 7.67 dd (1H), *J* = 0.9, 8.1
20a	4.15 (5H)	4.14 (1H), 4.18 (1H), 4.31 (2H)	2.31 s (3H), 3.68 m (1H), 3.85 s (3H), 4.90 d (1H), *J* = 6.9	2.05 m (1H), 2.43 m.(1H), 3.03 m (1H), 3.18 m (1H)	6.75 d (1H), *J* = 2.7; 6.85 dd (1H), *J* = 2.7, 8.7; 7.82 d (1H), *J* = 8.7
21a	4.16 (5H)	4.13 (1H), 4.18 (1H), 4.20 (1H), 4.44 (1H)	2.32 s (3H), 3.69 m (1H), 3.87 s (3H), 4.94 d (1H), *J* = 6.91	2.04 m (1H), 2.44 m (1H), 3.01 m (1H), 3.13 m (1H)	6.95 dd (1H), *J* = 2.7, 8.4; 7.16 d (1H), *J* = 8.4; 7.36 d (1H), *J* = 2.7
22a	4.16 (5H)	4.09 (1H), 4.16 (1H), 4.19 (1H), 4.44 (1H)	2.27 s (3H), 2.32 s (3H), 2.35 s (3H), 3.64 m (1H), 4.94 d (1H), *J* = 6.3	2.01 m (1H), 2.47 m (1H), 2.86-3.00 m (2H)	7.08 s (1H), 7.56 s (1H)
22b	4.24 (5H)	4.02 (1H), 4.11 (1H), 4.14 (1H), 4.19 (1H)	2.17 s (3H), 2.27 s (3H), 2.32 s (3H), 3.80 m (1H), 5.61 d (1H), *J* = 9.34	1.92 m (1H), 2.39 m (1H), 3.07 m (1H), 3.12 m (1H)	7.01 s (1H), 7.75 s (1H)
23a	4.15 (5H)	4.11 (1H), 4.17 (1H), 4.19 (1H), 44.43 (1H)	1.46 d (3H), *J* = 6.9, 2.31 s (3H), 3.28 m (1H), 3.74 m (1H), 4.93 d (1H), *J* = 6.32	1.82 m (1H), 2.45 m (1H)	7.30 m (1H), 7.41 dd (2H), *J* = 1.2, 8.4; 7.87 d (1H), *J* = 8.4
23b	4.18 (5H)	4.02 (1H), 4.13 (1H), 4.17 (1H), 4.23 (1H)	1.55 d (3H), *J* = 7.5; 2.32 s (3H), 3.40 m (1H), 3.91 m (1H), 5.62 d (1H), *J* = 9.32	1.74 m (1H), 2.26 m (1H)	m (1H), 7.44 dd (2H), *J* = 0.9, 8.3; 7.84 dd (1H), *J* = 0.9, 8.3
24a	4.15 (5H)	4.13 (1H), 4.17 (1H), 4.19 (1H), 4.44 (1H)	2.32 s (3H), 3.71 m (1H), 4.94 d (1H), *J* = 6.9	2.03 m (1H), 2.43 m (1H), 3.06 m (1H), 3.19 m (1H)	7.23 - 7.36 m (3H), 7.88 dd (1H), *J* = 1.2, 7.8
24b	4.23 (5H)	4.06 (1H), 4.14 (2H), 4.19 (1H)	2.31 s (3H), 3.80 m (1H), 5.63 d (1H), *J* = 9.9	1.98 m (1H), 2.37 m (1H), 3.07 m (1H), 3.23 m (1H)	7.30 - 7.40 m (3H), 7.87 d (1H), *J* = 8.0

According to ^{1}H NMR spectroscopy, the chemical shifts of the H(3) protons at the C(3) atoms of the dihydropyrazole fragments in the tricyclic pyrazoles type **a** (**19a-24a**) (see Table 1) have close values at δ 4.9 ppm and $^3J_{H(3),H(3a)}$ = 6.3 – 6.9 Hz, respectively. The chemical shifts of the analogous protons in the diastereomers type **b** (**19b,22b-24b**) are observed at lower fields (δ 5.6 ppm) and larger values of

$^{3}J_{H(3),H(3a)}$ = 9.3 - 9.9 Hz. These data are supported from the reported values.[6,7]

Table 2. ^{13}C-NMR spectral data of compounds (**7, 12, 19a,b**, **20a** and **21a**) (δ, ppm)

Compound	C_5H_5	C_5H_4	$C_{ipso}Fc$	CH_2, CH_3	CH	Ar	C=N, C=O	C
7	69.5	70.6, 70.9	79.2	21.0, 26.32, 55.7	113.9	119.8, 127.0, 137.1	187.0	131.1, 132.1, 134.9, 156.1
12	69.4	70.6, 70.9	79.1	26.8, 28.4	126.8	127.9, 128.0, 132.7, 137.4	186.8	131.0, 133.8, 143.03
19a	68.2	66.1, 67.9, 68.1, 70.5	88.2	22.3, 23.6, 28.9, 55.4	52.8, 61.1	111.0, 116.7, 127.29	157.1, 170.0	127.9, 129.1, 156.04
19b	69.3	65.3, 67.0 67.7, 67.9	86.4	22.5, 22.72, 28.9, 58.48	49.0, 61.1	111.3, 116.7, 126.88	157.2, 172.0	127.9, 132.0, 156.1
20a	68.2	66.3, 67.9, 68.2, 70.4	88.4	22.3, 29.42, 29.9, 55.36	53.5, 60.9	113.1, 135,2 113.3, 126.4	161.1, 170.1	120.8, 140.8, 155.53
21a	68.2	66.2, 68.0, 68.2, 70.5	88.2	22.3, 28.86, 29.8, 55.50	53.3, 61.2	107.8, 17.8, 130.1	158.2, 170.2	128.8, 131.4, 155.95

Table 3. Elemental analysis data, yields and mp for the synthesized compounds

Comp. No.	R_1	R_2	R_3	R_4	Yield %	mp °C	Found % / Calcd. % C	H	Fe	N	Molecular formula
7	H	OCH_3	H	H	71	150-151	70.78 / 70.98	5.64 / 5.42	14.77 / 15.00		$C_{22}H_{20}FeO_2$
8	H	H	OCH_3	H	68	112-113	71.04 / 70.98	5.27 / 5.42	15.09 / 15.00		$C_{22}H_{20}FeO_2$
9	H	H	H	OCH_3	72	138-139	70.81 / 70.98	5.53 / 5.42	15.16 / 15.00		$C_{22}H_{20}FeO_2$
10	H	CH_3	H	CH_3	75	116-117	74.42 / 74.60	5.79 / 6.00	15.24 / 15.08		$C_{23}H_{22}FeO$
11	CH_3	H	H	H	67	106-107	73.99 / 74.17	5.85 / 5.66	15.54 / 15.67		$C_{22}H_{20}FeO$
12	H	H	H	H	72	156-158*	73.53 / 73.70	5.48 / 5.30	16.46 / 16.32		$C_{21}H_{18}FeO$
13	H	OCH_3	H	H	72	184-187	68.73 / 68.41	5.96 / 5.74	14.75 / 14.46	7.53 / 7.25	$C_{22}H_{22}FeN_2O$
14	H	H	OCH_3	H	71	191-193	68.18 / 68.41	5.49 / 5.74	14.64 / 14.46	7.49 / 7.25	$C_{22}H_{22}FeN_2O$
15	H	H	H	OCH_3	70	283-284	68.65 / 68.41	5.87 / 5.74	14.19 / 14.46	7.04 / 7.25	$C_{22}H_{22}FeN_2O$
16	H	CH_3	H	CH_3	69	202-204	71.63 / 71.88	6.57 / 6.30	14.84 / 14.53	7.43 / 7.29	$C_{23}H_{24}FeN_2$
17	CH_3	H	H	H	70	172-174	71.09 / 71.36	5.76 / 6.00	14.79 / 15.08	7.79 / 7.56	$C_{22}H_{22}FeN_2$
18	H	H	H	H	70	168-170	70.53 / 70.80	5.91 / 5.66	15.41 / 15.68	7.61 / 7.86	$C_{21}H_{18}FeO$
19a	H	OCH_3	H	H	48	194-195	67.12 / 67.30	5.83 / 5.66	13.31 / 13.04	6.70 / 6.54	$C_{24}H_{24}FeN_2O_2$
19b	H	OCH_3	H	H	6	186-188	67.43 / 67.30	5.43 / 5.66	13.20 / 13.04	6.41 / 6.54	$C_{24}H_{24}FeN_2O_2$
20a	H	H	OCH_3	H	69	180-181	67.15 / 67.30	5.79 / 5.66	12.96 / 13.04	6.69 / 6.54	$C_{24}H_{24}FeN_2O_2$
21a	H	H	H	OCH_3	72	173-174	67.47 / 67.30	5.48 / 5.66	13.23 / 13.04	6.73 / 6.54	$C_{24}H_{24}FeN_2O_2$
22a,b	H	CH_3	H	CH_3	71	187-188	70.28 / 70.43	6.23 / 6.15	13.01 / 13.10	6.71 / 6.57	$C_{25}H_{26}FeN_2O$
23a,b	CH_3	H	H	H	71	128-129	69.74 / 69.91	5.99 / 5.86	13.36 / 13.55	6.92 / 6.79	$C_{24}H_{24}FeN_2O$
24a,b	H	H	H	H	74	164-165	69.54 / 69.36	5.39 / 5.57	13.88 / 14.02	6.91 / 7.03	$C_{23}H_{22}FeN_2O$

* ref.[21] mp 154 °C

We managed to isolate individual isomers (**19a** and **19b**) by multiple crystallization and preparative TLC on alumina plate. The yields of the pure isomers, their melting points and elemental analysis data are listed in Table 3.

The independent structural determination for compound (**19b**) was performed by X-Ray analysis (Table 4).

Table 4**.** Crystal data, data collection and refinement parameters for (**19b**)

Data	**19b**
Molecular formula	$C_{20}H_{23}N_3OFe$
Molecular weight	377.26
Temperature (K)	293
Crystal system	Ortorombic
Space group	Pbca
a (Å)	18.174(3)
b (Å)	9.034(1)
c (Å)	20.853(2)
α (°)	90.0
β (°)	90.0
γ (°)	90.0
V (Å^3)	3423.7(8)
Z	8
ρ_{calc}/g cm^{-3}	1.464
Absorption coefficient (mm^{-1})	0.894
F(000)	1584
λ /Å (Mo-Kα radiation)	0.71073
Monochromator	Graphite
Θ scanning range/deg	1.50 - 25.00
Total number of reflections	3845
Number of independent reflections	3012
R_{int}	0.0434
Number of refinable parameters	296
Goodness of fit	1.023 (full-matrix least-squares refinement on F^2)
Residual electron density/e·Å^{-3}, ρ_{min}/ρ_{max}	-0.327/ 0.441
Weighting scheme	$w^{-1} = \sigma^2(Fo^2) + (0.0735P)^2$, where $P = (Fo^2 + 2Fc^2)/3$

The general view of the molecule (**19b**) is shown in Figure 1. The pivotal element of the molecule (**19b**) is the tricyclic framework of a five-membered pyrazoline in the form of a flattened envelope fused with a bicyclic carbocycle of the 1,2,3,4-tetrahydronaphthalene. The ferrocenyl substituent occupies a pseudoaxial position. The hydrogen atoms H(3a) at C(3a) and H(3) at C(3) are *trans* oriented. The N(1)=C(9b) bond on the pyrazoline ring is somewhat longer, and the N(1)-N(2) bond is somewhat shorter compared to that of the standard lengths (cf. *d* (C=N) 1.23 Å[17] and *d* (N-N) 1.45 Å[18]). The Fe-C, C-C and C=C bond and geometry of the ferrocenyl sandwiches in the isomer (**19b**) have ordinary parameters.

Based on the X-Ray diffraction data for pyrazoline (**19b**) and the ^{1}H-NMR spectra of diastereomeric compounds (**19a-24a**) and (**19b, 22b-24b**), type **a** structures were referred to as *cis* isomers and type **b** structures were assigned to the *trans* isomers.

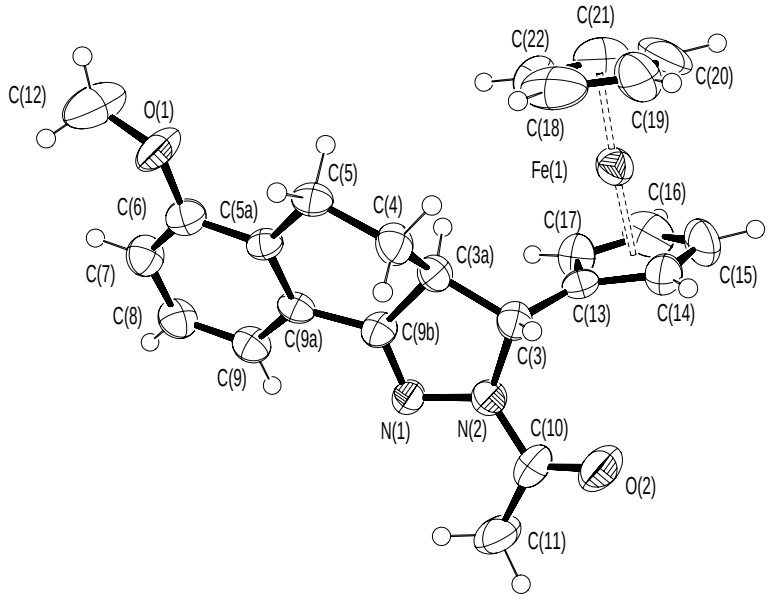


Figure 1. Crystal structure of **19b**. Selected bond lengths (Å): N(1)-N(2) = 1.421(4); N(1)-C(9b) = 1.276(4); C(3a)-C(4) = 1.500(4); N(2)-C(3) = 1.508(4); N(2)-C(10) = 1.494(5); C(3)-C(3a) = 1.540(6).

The ratio between isomers **a** and **b** was determined more accurately from the NMR spectra of specimens isolated from the reaction mixtures. which gives an idea of the effect of the chiral elements in the starting enones on the diastereoselectivity of formation of pyrazolines (**19-24**), these data are listed in Table 5.

Table 5. Diastereoselectivity in the synthesis of compounds (**19-24**)

Direction of synthesis	Integral intensity **a** H(3) **: b** H(3)	Diastereomer yield (%) **a**	**b**	Diastereoselectivity (%)
7→19	6 : 1	85	15	70
8→20	1 : 0	100	0	100
9→21	1 : 0	100	0	100
10→22	16 : 1	94	6	88
11→23	19 : 1	95	5	90
12→24	9 : 1	90	10	80

Effect of the test compounds on TPA induced inflammation

The assay of TPA-induced ear edema in mice was perfomed as described previously.[19] Groups of 5-8 CD-1 male mice (25-30 g each specimen) were anaesthetized with Imalgen®. A solution of 12-O-tetradecanoylphorbol-13-acetate (TPA, 2.5 μg) dissolved in ethanol (10 μL) was topically applied to both sides (5 μL each side) of the right ear of the mice. The left ear received only 10 μL of ethanol. Solutions of samples (**7-12** and **19-24**) and indomethacine as reference, dissolved in CH_2Cl_2 and acetone, respectively, were applied to both sides of the right ear (10 μL each side) 10 min after TPA treatment.

Control animals received only the appropriate solvent. Four hours later the animals were killed by cervical dislocation and a plug (9 mm in diameter) was removed from both treated and the untreated ear. The difference in weight between the two plugs was taken as a measure of the edematous response. The % inhibition of edema is defined by the following equation:

$$\% \text{ Inhibition} = (Cr-Ct)/(Cr) \times 100$$

where Cr is the edema response in TPA alone and Ct is the edema response plus sample groups. Results of increase in weight are expressed as percentages of inhibition of n=5-8 animals. One–way analysis of variance followed by Dunnett's test to compare several groups with the control, analyzed all data. Inhibitory concentrations (IC_{50}) were calculated from at least three significant concentrations for a regression analysis, each point being the mean of the percentage inhibition at the given dose, from two independent experiments; 98 % confidence limits were calculated with a standard calculation program.[20] The effect of the compounds on the TPA induced edema is shown in Table 6.

Table 6. Edema inhibition (%) for the compounds (**7-12** and **19-24**)

Compound	**0.031 mg/ear** (% ± ES)	**0.1 mg/ear** (% ± ES)	**0.31 mg/ear** (% ± ES)	**1 mg/ear** (% ± ES)	**IC_{50} mg/ear** (r)
Indometacine (reference)	48 ± 15 *	60 ± 10 *	88 ± 4 *	91 ± 2 *	0.036 (0.95)
7	25 ± 9	43 ± 7 *	53 ± 8 *	63 ± 10 *	0.27 (0.99)
8	24 ± 14	26 ± 10 *	61 ± 14 *	83 ± 6 *	0.24 (0.98)
9	7 ± 4	26 ± 5 *	50 ± 7 *	62 ± 16 *	0.41 (0.98)
10	9 ± 6	23 ± 3 *	59 ± 9 *	76 ± 9 *	0.28 (0.97)
11	0	9 ± 5	33 ± 4 *	38 ± 2 *	> 1
12	0	33 ± 4 *	51 ± 11 *	73 ± 5 *	0.27 (0.99)
19a,b	25 ± 9	39 ± 9 *	68 ± 7 *	66 ± 8 *	0.13 (0.98)
20a	6 ± 7	44 ± 12 *	59 ± 11 *	79 ± 6 *	0.16 (0.99)
21a	13 ± 10	35 ± 6 *	62 ± 11 *	70 ± 12 *	0.22 (0.98)
22a,b	15 ± 9	50 ± 4 *	68 ± 7 *	85 ± 2 *	0.09 (0.98)
23a,b	10 ± 16	14 ± 4	33 ± 7 *	76 ± 5 *	ND
24a,b	7 ± 4	35 ± 7 *	75 ± 8 *	80 ± 5 *	0.16 (0.90)

ND= Not determined; * $P \leq 0.05$ Dunnett's test

All the tested compounds, with the exception of the compound (**11**), showed moderate anti-inflammatory activity, similar to that of the indometacine. It was not possible to observe any differences in the biological activity of the diastereoisomers **a** and **b**. Compound (**11**) showed low anti-inflammatory activity.

CONCLUSIONS

In the synthesis of ferrocenyl diazatricyclo tetraenes, we observed an asymmetrical induction of the chiral center-chiral center due to the presence of the ferrocenyl groups in the molecule. This favored the formation of the *cis* diasteroisomers in larger amounts. All the synthesized compounds, with the exception of the compound (**11**), showed moderate anti-inflammatory activity, similar to that of the indometacine.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were registered in $CDCI_3$ on a 'Unity Inova Varian' spectrometer (300 and 75 MHz) using Me_4Si as the internal standard. Column chromatography was carried out on Al_2O_3 (activity III according to Brockmann). Were used reagents of the firm "Aldrich" (ferrocenecarboxaldehyde, 98%; 5-methoxy-1-tetralone, 97%; 6-methoxy-1-tetralone, 99%; 7-methoxy-1-tetralone, 99%; 5,7-dimethyl-1-tetralone, 97%; α-tetralone, 98%;hydrazine monohydrate, 98%).

The data from the elemental analyses for the obtained substances, their yields and mp are listed in Table 3.

Synthesis of α,β-enones. General procedure

α,β-Enones were synthesized starting from ferrocenecarboxaldehyde and tetralone in the presence of NaOH in aqueous EtOH. The reaction mixture was rapidly poured in water (200 mL), the precipitate that formed was filtered off, washed with water on a filter, and dried in vacuo. Additional purification was achieved by chromatography on a column with alumina or recrystallization from benzene.

E-2-Ferrocenylmethylidene-5-methoxy-1-tetralone (**7**) was obtained by a conventional procedure[16] starting from ferrocenecarboxaldehyde and 5-methoxy-1-tetralone in the presence of alkali in aqueous EtOH. *E*-2-Ferrocenylmethylidene-6-methoxy-1-tetralone (**8**), *E*-2-ferrocenylmethylidene-7-methoxy-1-tetralone (**9**), *E*-2-ferrocenylmethylidene-5,7-dimethyl-1-tetralone (**10**), *E*-2-ferrocenylmethylidene-4-methyl-1-tetralone (**11**) and *E*-2-ferrocenylmethylidene-1-tetralone (**12**) were synthesized analogously.

3-Ferrocenyl-6-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**13**) was synthesized by the following procedure. Hydrazine hydrate (5 mL) was added to a solution of enone (**7**) (1.23 g, 3.3 mmol) in EtOH (40 mL) and the mixture was heated at 70 ^{o}C and stirred for 3 h. After that was cooled, and yellow crystals of

dihydropyrazole (**13**) that sedimented were filtered off, washed with aqueous EtOH, and dried over P_2O_5. 3-Ferrocenyl-7-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**14**), 3-ferrocenyl-8-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**15**), 3-ferrocenyl-6,8-dimethyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**16**), 3-ferrocenyl-5-methyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**17**) and 3-ferrocenyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**18**) were obtained analogously from the corresponding enones (**8-12**).

***N*-Acetylindazoles (19-24)**

N-Acetyldihydropyrazoles (**19-24**) were synthesized using the following general procedure. Dry indazoles (**13-18**) (3.3 mmol) were dissolved in acetic anhydride (2 mL). The reaction mixture was stirred for 1 h at ambient temperature and then treated with 5% aqueous Na_2CO_3. Yellow crystals were filtered off, washed with aqueous EtOH, and dried over P_2O_5. 2-Acetyl-3-ferrocenyl-6-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**19a**+**19b**, ~6:1), 2-acetyl-3-ferrocenyl-7-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**20a**), 2-acetyl-3-ferrocenyl-8-methoxy-3,3a,4,5-tetrahydro- 2*H*-benzo[*g*]indazole (**21a**), 2-acetyl-3-ferrocenyl-6,8-dimethyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**22a**+**22b**,~16:1), 2-acetyl-3-ferrocenyl-5-methyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**23a**+**23b**, ~19:1) and 2-acetyl-3-ferrocenyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (**24a**+**24b**, ~9:1) were synthesized analogously. Pure isomer (**19a**) was isolated by crystallization from ethanol. The mother liquor was subjected to TLC on alumina (hexane-benzene, 1:1), which made it possible to separate diastereomers (**19a** and **19b**): (**19a**), R_f = 0.67; (**19b**), R_f = 0.51.

Before determination of biological activity compounds (**7-12**, **19a**,**b**, **20a**, **21a**, and **22a**,**b-24a**) were purified by column chromatography on Al_2O_3 and recrystallized from ethanol. The data from the biological activity results for the obtained substances are listed in Table 6.

Crystal structure determination

The unit cell parameters and the X-Ray diffraction intensities were recorded on a Siemens P4/PC/ω diffractometer. The structure of compound (**19b**) was solved by the direct method (SHELXS) and refined using full-matrix least-squares on F^2. CCDC reference number 231453 for compound (**19b**). See http://www.rsc.org/suppdata/ for crystallographic data in .cif or other electronic format.

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