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Synthesis and structure of planar chiral ferroceno[*d*]pyridazinones, the first representatives of a novel class of fused metallocenes

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ABSTRACT

A series of planar chiral ferroceno[*d*]pyridazinones was prepared by hydrazine-mediated cyclisations of (S_p)-2-formylferrocenoyl fluoride obtained in two steps from (2S,4S)-4-(methoxymethyl)-2-ferrocenyl-1,3-dioxane. Further derivatives based on the novel heterocyclic scaffold were resulted by means of the facile N-alkylation reactions carried out on the easily accessible fused product derived from the hydrazine-mediated cyclisation. Upon treatment with hydrazine (S_p)-2-formylferroce carboxylic acid, the precursor of the acid fluoride with enhanced reactivity, afforded a dimeric azine avoiding cyclisation. The spectacular difference between the experimentally observed reactivity of the bifunctional formylferrocenes was disclosed by comparative DFT analysis of the assumed hydrazone- and hydrazide intermediates with different values of LUMO energy associated with different conformation. The structures of the new compounds were established by IR and NMR spectroscopy, including HMQC, HMBC and DNOE measurements.

1. Introduction

During the last decades the chemistry of ferrocenes has attracted remarkable attention due to their wide range of interest in material sciences, catalysis and biological assays [1]. Besides these applications the sandwich complexes have also been shown different biological activities and were also used in therapy [2]. Earlier, our group have synthesized and characterized different ferrocene-containing heterocycles of potential and – in a few cases [3e] - proved biological activity, including ferrocenyl-pyrazoles- and pyrazolines-, condensed 1,2,4-triazoles- [3], imidazoles- [4], diazepines- [5], oxazoles- [6], dihydropyrimidines [7], quinolines [8] and pyridazines [9]. On the other hand, according to the literature a wide variety of heterocyclic scaffolds possess valuable pharmaceutic properties including anticancer effects [10], however much less attention has been paid to the chemistry of ferrocene-condensed heterocycles offering the possibility to introduce planar chirality into the molecule [11]. Prompted by this fact, in the frame of our ongoing research on ferrocene-containing heterocyclic compounds to be tested in *in vitro* assays we targeted the preparation of the first representatives of ferroceno[*d*]pyridazines, a new class of heterocyclic ring system of potential biological relevance.

2. Results and discussion

2.1. Synthesis of ferroceno[d]pyridazinones

First chiral ferrocenyl dioxane **1** was prepared from formyferrocene in two steps according to the protocol described by Kagan et al. [12] which was then transformed into carboxylic acid **2** by directed diastereoselective lithiation [12] followed by carboxylation (Scheme 1). We envisaged the hydrazine-mediated cyclisation of **2** to obtain ferroceno[*d*]pyridazione **5a** which can be considered as the precursor of a variety of N-alkylated derivatives. Contrary to our expectations the reaction conducted in refluxing ethanol afforded dimer **3** in good yield (82%) without being contaminated by pyridazinone product. When a five-fold excess of hydrazine hydrate was used as reagent **3** could again be isolated from the reaction mixture. This observation is in accord with the facile hydrazine-mediated conversion of formylferrocene yielding dimmer azine [13]. Employing the same conditions ring closure of **2** was also attempted with methyl- and (2-hydroxyethyl)-hydrazine, respectively, but the reactions gave undefined decomposition products. Since the carboxyl group seemed to be deactivated by the highly electron-releasing ferrocene moiety [14], **2** was converted into acid fluoride **4** by treatment with cyanuricfluoride and pyridine in DCM [15]. To our pleasure **4** could be isolated in unexpectedly high yield (85%) which was converted into the first targeted ferroceno[*d*]pyridazinone **5a** in good yield (77%) on short treatment (10 min) with hydrazine hydrate in dry THF at

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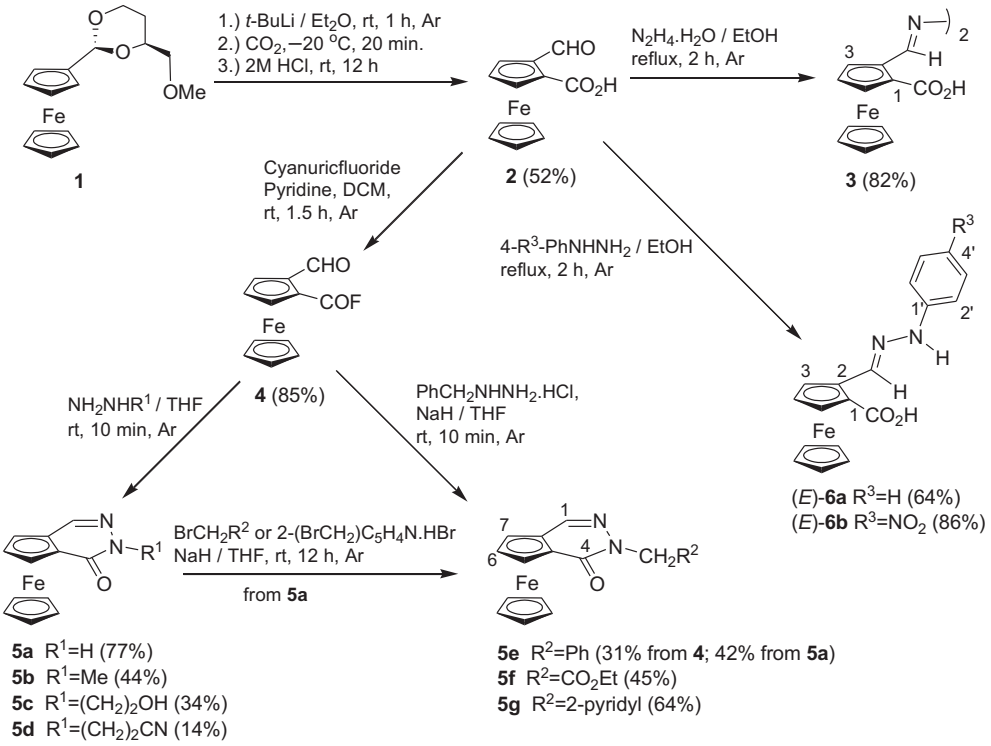

Scheme 1. Synthesis and subsequent transformations of planar chiral bifunctional ferrocenes including the synthesis of ferrocenopyridazinones.

room temperature. The reactions employing alkylhydrazine-type reagents gave the corresponding N3-alkylated pyridazinones **5b**–**e** in substantially lower yields (14–44%) which could not be increased by employing prolonged reaction time (1 h) and elevated temperature (50–60 °C) due to the formation of the mixture of undefined tarry materials. On the other hand, the N-alkylation reactions of the easily accessible **5a** with bezylbromide, 2-bromomethylpyridine and ethyl bromoacetate (**5a**→**5e**–**g**: Scheme 1) carried out under basic conditions (NaH/THF) at room temperature demonstrated an alternative synthetic route to versatile products containing the novel metallocene scaffold.

Attempted cyclisations of **4** with phenylhydrazine and 4-nitrophenylhydrazine, respectively, carried out in THF at room temperature led also to the formation of complex mixtures. Employing the same reagents in refluxing ethanol **2** afforded hydrazones (*E*)-**6a,b** (Scheme 1) which – on prolonged heating in the different mixtures of EtOH and AcOH – underwent decomposition reactions.

2.2. Comparative theoretical study on the structure and reactivity of the possible intermediates involved in the cyclisation reactions

Prompted by the fact that in pure organic chemistry 2-formylbenzoic acid and related bifunctional precursors can easily be converted into condensed pyridazinones on the effect of hydrazines [16], we undertook DFT modelling [17] to interpret the reluctance of **2** and the enhanced reactivity of **4** to undergo analogous heterocyclisation. The optimized global minimum structures of three hydrazones with (*Z*) configuration **7**, **8** and **9**, the assumed intermediates of the hydrazine-mediated cyclisation reactions of 2-formylbenzoic acid, **2** and **4** (Fig. 1), were obtained by B3LYP calculations [18] using 6–31 G(d) basis set [19]. The energy values of LUMO characterising the reactivity of the carbonyl group are in good correlation with the crucial $\underline{NH_2}$–$\underline{C}O$ distance and the above-mentioned preparative observations suggesting that the pronounced deactivating effect of the ferrocene moiety on the electrophilic centre, reflected by the calculated data of **8**, is at least partly compensated by the fluorine atom in **9**.

Since the cyclisations of type **4**→**5** can also be assumed to proceed in a competitive manner *via* primary N-acylation followed by condensation with the formyl group hydrazide **10**, the intermediate of the reaction of **4** effected by hydrazine hydrate, was also subjected to DFT analysis (Fig. 1). Suggesting its facile ring closure the LUMO energy and the $\underline{NH_2}$–$\underline{C}O$ distance obtained for the optimized structure are in line with the same parameters calculated for hydrazones **7**–**9**.

2.3. Structure determination of the novel compounds

The spectroscopic data listed in the Experimental Part are consistent with the structures of **2**, **3**, **4**, **5a**–**g** and (*E*)-**6a**,**b** only the following remarks are necessary.

Both ^1H and ^{13}C NMR spectra taken of **2** in DMSO-d_6 solution point to the presence of formyl- and carboxyl groups excluding the detectable formation of the cyclic hydroxylacton isomer.

Interestingly, in $CDCl_3$ solution **4** proved stable enough to be subjected to longer NMR measurements. In its ^{13}C NMR spectrum a considerable split of the line of the carbonyl group directly attached to fluorine ($^1J_{C\text{-}F}$ = 336.3 Hz) was detected, while the doublets of the C1 and C2 signals point to weaker interactions with the fluorine atom ($^2J_{C\text{-}F}$ = 72.4 Hz and $^3J_{C\text{-}F}$ = 4.6 Hz, respectively).

As the consequence of planar chirality the diastereotopic protons of the CH_2 group attached directly to N3 atom in **5b**–**g** produce separated signals.

The characteristic cross peak due to the ^3J coupling between the NH proton and C4a atom detected in the ^1H-^{13}C-HMBC spectrum of **5a** indicates the condensation of the pyridazinone ring to the ferrocene moiety.

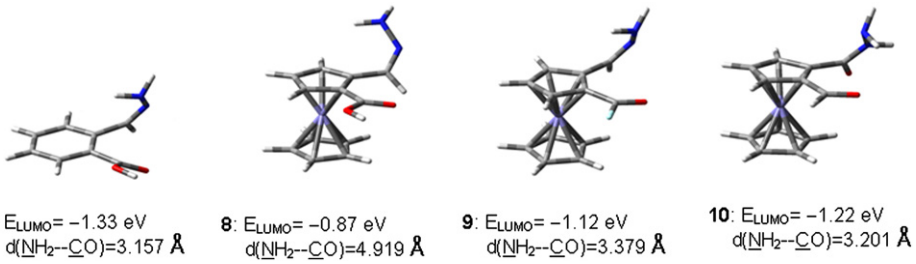

Fig. 1. Optimized structures with characteristic NH_2–CO distance and E_{LUMO} of hydrazones (*Z*)-**7**–**9** and hydrazide **10** (*for the sake of unique, comparable appearance the enantiomeric form is represented*), the assumed intermediates of the heterocyclisations of 2-formylbenzoic acid, **2** and **4**.

The (*E*) configuration at the C=N bond in **6a**,**b** was unambiguously evidenced by the mutual NOE's (6–9%) detected between the NH and CH protons.

For **5a**–**g** the assignment of the skeletal protons is based on NOE's (4–6%) detected for the proton pairs H1/H7, H7/H6 and H6/H5.

In the ^{1}H-^{15}N HMBC spectra of **5a**–**g** the H1 signal gives correlation with the signals of N2- and N3 atoms discernible at 320 ± 2 ppm and 180 ± 3 ppm, respectively, unambiguously suggesting the presence of adjacent imino- and lactam groups. Both N2 and N3 signals are also correlated with the protons of the CH_3- or CH_2 group directly attached to N3 (in **5b**–**g**). In the spectrum of **5a** the correlation between nuclei H3 and N3 appears as a satellite signal reflecting a coupling constant of 95 Hz ($^1J_{N\text{-}H}$).

Due to the enhanced delocalisation of the lone pair from the NH group towards the nitro substituent transmitted by the phenyl ring, the corresponding signal is downfield shifted in (*E*)-**6b** (153 ppm) relative to that measured for (*E*)-**6a** (142 ppm).

3. Conclusion

By extending the groups of hydrazine reagents and alkylating agents the reported syntheses of the first representatives of planar chiral ferroceno[*d*]pyridazinones based on 2-formylferrocenecarbonyl fluoride might open up expedient ways to a wide variety of novel metallocene derivatives of potential biological interest. Alkylation with multifunctional reagents can be followed by further transformations resulting in novel molecular libraries of diverse structures. The easily accessible 2-formylferrocenecarbonyl fluoride of which preparation is described in this contribution can be considered as the precursor of a range of metallocene scaffolds with planar chirality. The structure-reactivity relationship disclosed for the hydrazone- and hydrazide intermediates by DFT modelling can also be taken into account to set up procedures for related cyclisation reactions targeting the synthesis of further fused ferrocenes.

4. Experimental

All chemicals were obtained from commercially available sources (Aldrich, Fluka) and – except for THF – used without further purification. THF was purified by subsequent distillations from $LiAlH_4$ and sodium benzophenone. Melting points (uncorrected) were determined with a Boethius microstage. Merck Kieselgel (230–400 mesh, 60 Å) and alumina (Brockmann I grade, approx. 150 mesh, 58 Å, activated neutral) were used for flash column chromatography. The IR spectra were run by ATR (Attenuated Total Reflectance) method [20] on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. Optical rotations were measured with a Zeiss Polamat A polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX-500 spectrometer at 500 (^{1}H), 125 (^{13}C) and 50 (^{15}N) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard (^{1}H, ^{13}C) and NH_3(liq) as external reference (^{15}N). The ^{15}N NMR chemical shifts were obtained and assigned from the ^{1}H–^{15}N HMBC spectra. DEPT spectra were run in a standard manner, using only a $\Theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-COSY, HSQC, HMBC and DIFFNOE spectra were obtained by using the standard Bruker pulse programs. All calculations were carried out with the Gaussian 03 suite of programs [21]. Optimized structures are available from the authors.

4.1. (S_p)-2-Formylferrocene-1-carboxylic acid (**2**)

In a dry Schlenk tube a solution of acetal **1** (6.32 g, 20 mmol) in dry degassed diethylether (90 mL) was treated with a pentane solution of *t*-butyllithium (1.7 M, 15.1 mL, 22 mmol) at −78 °C for 10 min. The reaction mixture was allowed to warm up to rt., stirred for 1 h and cooled down to −20 °C. At this temperature dry CO_2 gas was introduced into the resulted orange suspension for 20 min to produce the precipitate of the lithium carboxylate salt. After the addition of 2 M HCl (30 mL) containing $SnCl_2$ (1 g) the solution was allowed to warm up to rt., stirred for overnight and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic phase was washed with water (3 × 40 mL), dried over Na_2SO_4, and evaporated. The oily residue was subjected to flash column chromatography on silica first using DCM-MeOH (80:1) as eluent to produce a fraction containing an undefined mixture. On repeated elution with DCM-MeOH 30:1 two bands developed on the standing phase. Evaporation of the first band gave recovered formylferrocene (0.770 g, 18%). The residue obtained by the evaporation of the second fraction was triturated with petroleum ether 40/70, filtered off and dried to give the product as a dark orange solid. Yield: 2.713 g (52%); mp.: 94–95 °C (decomp.); $[\alpha]_D^{25}$: +24.5° (EtOH); IR (cm^{-1}): ~3300–2500, 1708, 1625, 1454, 1213, 1174, 701; ^{1}H NMR (DMSO-d_6): 10.05 (s, 1H, CH=O); 5.14 (br s, 1H, H3); 5.02 (br s, 1H, H4); 4.91 (br s, 1H, H5); 4.37 (s, 5H, η^5-C_5H_5); ^{13}C NMR (DMSO-d_6): 194.3 (CH=O); 172.3 (CO_2H); 80.3 (C2); 77.1 (C3); 75.2 (C1); 74.9 (C4); 72.2 (η^5-C_5H_5); 71.8 (C5); Anal. Calcd. for $C_{12}H_{10}FeO_3$ (258.05): C: 55.85; H: 3.91; Found: C: 55.71; H: 4.03%.

4.2. General procedure for the reactions of **2** with hydrazines

(S_p)-2-Formylferrocenecarboxylic acid (0.516 g, 2 mmol) and the corresponding hydrazine (2.2 mmol) were dissolved in ethanol (20 mL) and the solution refluxed for 2 h under Ar. After evaporation of the solvent and addition of water (10 mL) and a few drops of acetic acid the residue was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated to obtain a solid which was crystallized with petrolether 40/70 and dried to give the product.

4.2.1. (S_p,S_p)-1,2-Bis-(2-carboxyferrocenylmethylydene) hydrazine (**3**)

Red powder. Yield: 0.420 g (82%). mp.: 200–202 °C (decomp.); $[\alpha]_D^{25}$: +41.3° (DMF/EtOH 2/1); IR (cm^{-1}): ~3200–2800, 1664, 1613, 1464, 1234, 1082, 825,742; ^{1}H NMR (DMSO-d_6): 9.05 (s, 1H, CH=N); 5.11 (br s, 1H, H3); 5.02 (br s, 1H, H5); 4.74 (br s, 1H, H4); 4.32 (s, 5H, η^5-C_5H_5); ^{13}C NMR (DMSO-d_6): 172.7 (CO_2H); 161.9 (CH=N); 79.6 (C4); 75.0 (C5); 73.5 (C3); 72.0 (η^5-C_5H_5); 71.5 (C5); 70.9 (C2); ^{15}N NMR (DMSO-d_6): 329 (CH=N); Anal. Calcd. for $C_{24}H_{20}Fe_2O_4$ (512.12): C: 55.29; H: 3.94; N: 5.47; Found: C: 55.13; H: 3.98; N: 5.51%.

4.2.2. (S_p)-(E)-2-(2-carboxyferrocenylmethylydene)-1-phenylhydrazine[(E)-**6a**]

Dark orange powder. Yield: 0.446 g (64%). mp.: 93–94 °C (decomp.); $[\alpha]_D^{25}$: −12.0° (DMSO); IR (cm^{-1}): ~3100–2700, 1679, 1599, 1494, 1287, 1257, 1171, 1000, 820, 747, 691; ^{1}H NMR (DMSO-d_6): 12.53 (br s, 1H, CO_2H); 10.22 (s, 1H, NH); 8.35 (s, 1H, CH=N); 7.14 (t, ^3J = 7.3 Hz, 2H, H3′5′); 6.94 (d, ^3J = 7.3 Hz, 2H, H2′6′); 6.65 (t, ^3J = 7.3 Hz, 1H, H4′); 5.01 (br s, 1H, H3); 4.81 (br s, 1H, H5); 4.54 (br s, 1H, H4); 4.17 (s, 5H, η^5-C_5H_5); ^{13}C NMR (DMSO-d_6): 173.4 (CO_2H); 146.8 (CH=N); 136.9 (C1′); 129.9 (C3′5′); 119.0 (C4′); 112.5 (C2′6′); 84.1 (C2); 72.6 (C4); 71.7 (C5); 71.4 (η^5-C_5H_5); 70.1 (C1); 69.3 (C3); ^{15}N NMR (DMSO-d_6): 324 (CH=N); 142 (NH); Anal. Calcd. for $C_{18}H_{16}FeN_2O_2$ (348.18): C: 62.09; H: 4.63; N: 8.05; Found: C: 61.98; H: 4.68; N: 8.11%.

4.2.3. (S_p)-(E)-2-(2-carboxyferrocenylmethylydene)-1-(4-nitrophenyl)hydrazine[(E)-**6b**]

Dark red powder. Yield: 0.676 g (86%). mp.: 210–212 °C (decomp.); $[\alpha]_D^{25}$: +37.2° (DMSO); IR (cm^{-1}): 3260, ~3200–2800, 1670, 1593, 1300, 1273, 1172, 1108, 1070, 1000, 835, 748; ^{1}H NMR (DMSO-d_6): 12.59 (br s, 1H, CO_2H); 11.27 (s, 1H, NH); 8.61 (s, 1H, CH=N); 8.12 (d, ^3J = 8.8 Hz, 2H, H3′5′); 7.08 (br d, ^3J = 8.8 Hz, 2H, H2′6′); 5.11 (br s, 1H, H3); 4.93 (br s, 1H, H5); 4.69 (br s, 1H, H4); 4.26 (s, 5H, η^5-C_5H_5); ^{13}C NMR (DMSO-d_6): 173.3 (CO_2H); 151.4 (C1′); 143.1 (CH=N); 138.7 (C4′); 127.1 (C3′5′); 111.7 (C2′6′); 82.2 (C2); 73.4 (C5); 72.5 (C4); 71.7 (η^5-C_5H_5); 71.2 (C1); 69.5 (C3); ^{15}N NMR (DMSO-d_6): 370 (NO_2); 315 (CH=N); 153 (NH); Anal. Calcd. for $C_{18}H_{15}FeN_3O_4$ (393.17): C: 54.99; H: 3.85; N: 10.69; Found: C: 55.04; H: 3.78; N: 10.81%.

4.3. (S_p)-2-formylferrocenoyl fluoride (**4**)

(S_p)-2-Formylferrocene-1-carboxylic acid (**2**) (2.581 g, 10 mmol) was dissolved in dry DCM (50 mL). To this solution pyridine (1.650 mL) and cyanuride fluoride (3.605 mL) were added at 0 °C. After a few minutes the cooling bath was removed and the mixture was stirred at rt for 90 min under Ar. After addition of crushed ice the resulted suspension was filtered, the organic phase was separated, washed with cold water (3 × 50 mL), dried over Na_2SO_4, filtered and evaporated. After a few minutes the dark oily residue solidified. The dark orange airstable crystals were collected and dried in vacuum exicator over P_2O_5 overnight at rt. (The product can be stored in PE flask at rt. practically without decomposition.) Yield: 2.211 g (85%); mp.: 113–114 °C (decomp.); $[\alpha]_D^{25}$: +34.8° (acetone); IR (cm^{-1}): 1789, 1670, 1418, 1274, 1207, 951, 857, 774; ^{1}H NMR ($CDCl_3$): 10.49 (s, 1H, CH=O); 5.34 (br s, 1H, H5); 5.18 (br s, 1H, H4); 4.96 (br s, 1H, H3); 4.44 (s, 5H, η^5-C_5H_5); ^{13}C NMR ($CDCl_3$): 193.3 (CH=O); 162.1 (d, $^1J_{C\text{-}F}$ = 336.3 Hz, COF); 80.9 (d, $^3J_{C\text{-}F}$ = 4.6 Hz, C2); 77.4 (C4); 76.1 (C3); 74.3 (br s, C5); 72.8 (η^5-C_5H_5); 65.8 (d, $^2J_{C\text{-}F}$ = 72.4 Hz, C1); Anal. Calcd. for $C_{12}H_9FFeO_2$ (260.04): C: 55.43; H: 3.49; Found: C: 55.48; H: 3.58%.

4.4. General procedure for the reactions of **4** with hydrazines: preparation of **5a–d**

(S_p)-2-Formylferrocenecarbonyl fluoride (0.774 g, 3 mmol) and the corresponding hydrazine (4 mmol) were dissolved in dry THF (10 mL) and the solution was stirred for 10 min at r.t. Following this period the dark red solid precipitated from the reaction mixtures resulted by the reactions of **4** with hydrazine hydrate and methylhydrazine, respectively, were extracted with DCM (2 × 10 mL) (**5a**) or with EtOAc (2 × 10 mL) (**5b**). The The DCM solution of **5a** was filtered through cellit. After the evaporation of the solutions of **5a** and **5b**, respectively, the residue was triturated with petroleum ether 40/70, filtered off and dried to obtain the product. The reaction mixtures resulted by the reactions of **4** with 2-hydrazinoethanol hydrazine and 3-hydrazinopropionitrile, respectively, were evaporated to dryness and the oily residues were subjected to column chromatography on neutral alumina using DCM as eluent. The residue obtained by the evaporation of the orange band was triturated with petroleum ether 40/70, filtered off and dried to give the product.

4.4.1. (S_p)-Ferroceno[d]pyridazin-4(3H)-one (**5a**)

Reddish orange powder. Yield: 0.587 g (77%); mp.: 157–160 °C (decomp.); $[\alpha]_D^{25}$: +60.5° (DMF-EtOH 3:2); IR (cm^{-1}): ~3200–2800, 1642, 1474, 1407, 1174, 1106, 841, 591; ^{1}H NMR (DMSO-d_6): 11.16 (s, 1H, NH); 8.16 (s, 1H, H1); 5.13 (br s, 1H, H5); 5.02 (br s, 1H, H7); 4.58 (br s, 1H, H6); 4.12 (s, 5H, η^5-C_5H_5); ^{13}C NMR (DMSO-d_6):167.1 (C4); 141.2 (C1); 79.7 (C7a); 74.5 (C4a); 74.1 (C6); 67.0 (C7); 66.7 (C5); 70.7 (η^5-C_5H_5); ^{15}N NMR (DMSO-d_6): 323 (N2); 183 (N3); Anal. Calcd. for $C_{12}H_{10}FeN_2O$ (254.07): C: 56.73; H: 3.97; N: 11.03; Found: C: 56.88; H: 4.08; N: 8.03%.

4.4.2. (S_p)-3-Methylferroceno[d]pyridazin-4(3H)-one (**5b**)

Orange powder. Yield: 0.354 g (44%); mp.: 101–103 °C (decomp.); $[\alpha]_D^{25}$: +50.4° (DMF-EtOH 1:1); IR (cm^{-1}): 2953, 2922, 2853, 1649, 1444, 1409, 1342, 1102, 828, 598; ^{1}H NMR ($CDCl_3$): 8.04 (s, 1H, H1); 5.24 (br s, 1H, H5); 4.79 (br s, 1H, H7); 4.44 (br s, 1H, H6); 4.10 (s, 5H, η^5-C_5H_5); 3.69 (NCH_3); ^{13}C NMR ($CDCl_3$): 166.4 (C4); 140.7 (C1); 79.1 (C7a); 74.8 (C4a); 73.9 (C6); 67.0 (C7); 65.8 (C5); 70.4 (η^5-C_5H_5); 38.6 (NCH_3); ^{15}N NMR ($CDCl_3$): 322 (N2); 177 (N3); Anal. Calcd. for $C_{13}H_{12}FeN_2O$ (268.09): C: 58.24; H: 4.51; N: 10.45; Found: C: 58.28; H: 4.44; N: 10.32%.

4.4.3. (S_p)-3-(2-hydroxyethyl)ferroceno[d]pyridazin-4(3H)-one (**5c**)

Orange powder. Yield: 0.286 g (32%); mp.: 105–107 °C (decomp.); $[\alpha]_D^{25}$: +63.7° (DMF-EtOH 1:1); IR (cm^{-1}): 3350, 3085, 2951, 2865, 1622, 1580, 1444, 1409, 1346, 1140, 1105, 815, 590; ^{1}H NMR (DMSO-d_6): 8.21 (s, 1H, H1); 5.16 (br s, 1H, H5); 5.02 (br s, 1H, H7); 4.71 (br s, 1H, OH); 4.59 (br s, 1H, H6); 4.20 (m, 1H, NCH_AH_B); 4.13 (s, 5H, η^5-C_5H_5); 3.94 (m, 1H, NCH_AH_B); 3.68 (t, ^3J = 5.9 Hz, 2H, CH_2OH); ^{13}C NMR (DMSO-d_6): 165.8 (C4); 141.2 (C1); 79.3 (C7a); 74.7 (C4a); 74.5 (C6); 67.1 (C7); 66.9 (C5); 70.9 (η^5-C_5H_5); 59.6 (CH_2OH); 51.8 (NCH_2); ^{15}N NMR ($CDCl_3$): 320 (N2); 178 (N3); Anal. Calcd. for $C_{14}H_{14}FeN_2O_2$ (298.12): C: 56.40; H: 4.73; N: 9.40; Found: C: 56.48; H: 4.70; N: 9.34%.

4.4.4. (S_p)-3-(2-cyanoethyl)ferroceno[d]pyridazin-4(3H)-one (**5d**)

Red powder. Yield: 0.129 g (14%); mp.: 117–120 °C (decomp.); $[\alpha]_D^{25}$: +77.2° (DMF-EtOH 1:1); IR (cm^{-1}): 2950, 2923, 2247, 1665, 1451, 1368, 1335, 1304, 1118, 1104, 815, 785; ^{1}H NMR ($CDCl_3$): 8.14 (s, 1H, H1); 5.36 (br s, 1H, H5); 4.87 (br s, 1H, H7); 4.58 (m, 1H, NCH_AH_B); 4.54 (br s, 1H, H6); 4.24 (m, 1H, NCH_AH_B); 4.18 (s, 5H, η^5-C_5H_5); 2.97 (t, ^3J = 5.9 Hz, 2H, CH_2CN); ^{13}C NMR ($CDCl_3$): 166.5 (C4); 142.0 (C1); 118.0 (CN); 78.7 (C7a); 74.3 (C6); 74.1 (C4a); 67.4 (C7);

66.4 (C5); 70.8 (η^5-$\underline{C}_5H_5$); 45.8 (N$\underline{C}H_2$); 17.5 ($\underline{C}H_2$CN); Anal. Calcd. for $C_{15}H_{13}FeN_3O$ (307.13): C: 58.66; H: 4.27; N: 13.68; Found: C: 58.64; H: 4.34; N: 13.74%.

4.5. Preparation of (S_p)-3-benzylferroceno[d]pyridazin-4(3H)-one (**5e**)

Sodium hydride (0.140 g, 60% in mineral oil) (3.5 mmol) washed with dry *n*-hexane three times was suspended in dry THF (10 mL). To this suspension bezylhydrazine hydrochloride (0.555 g, 3.5 mmol) and (S_p)-2-formylferrocenecarbonyl fluoride (0.774 g, 3 mmol) were added in this sequence. The resulted mixture was stirred for 10 min at room temperature and evaporated to dryness. The residue was chromatographed on neutral alumina using DCM-MeOH (80:1) as eluent. The reddish orange band was collected and evaporated to obtain an orange thick oil which solidified on trituration with petroleum ether 40/70. The suspension was filtered off and dried to give **5e** as an orange powder. Yield: 0.320 g, (31%); mp.: 93–95 °C (decomp.); $[\alpha]_D^{25}$: −12.4° (DMSO); IR (cm^{-1}): 2956, 2923, 2858, 1657, 1581, 1493, 1447, 1330, 1105, 1001, 820, 736; 697; ^{1}H NMR ($CDCl_3$): 8.13 (s, 1H, H1); 7.51 (d, ^3J = 7.3 Hz, 2H, H2′6′); 7.42 (t, ^3J = 7.3 Hz, 1H, H4′); 7.35 (t, ^3J = 7.3 Hz, 2H, H3′5′); 5.52 (d, ^2J = 14.8 Hz, 1H, NC$\underline{H}_A$H$_B$); 5.29 (br s, 1H, H5); 5.12 (d, ^2J = 14.8 Hz, 1H, NCH$_A\underline{H}_B$); 4.84 (br s, 1H, H7); 4.50 (br s, 1H, H6); 4.01 (s, 5H, η^5-$C_5\underline{H}_5$); ^{13}C NMR ($CDCl_3$): 166.1 (C4); 141.2 (C1); 138.2 (C1′); 129.0 (C3′5′); 128.9 (C2′6′); 128.0 (C4′); 79.0 (C7a); 74.9 (C6); 74.0 (C4a); 67.3 (C7); 66.0 (C5); 70.5 (η^5-$\underline{C}_5H_5$); 53.9 (N$\underline{C}H_2$); ^{15}N NMR ($CDCl_3$): 321 (N2); 178 (N3); Anal. Calcd. for $C_{19}H_{16}FeN_2O$ (344.19): C: 66.30; H: 4.69; N: 8.14; Found: C: 66.44; H: 4.56; N: 8.06%.

4.6. Preparation of ***5ef*** by the alkylation of ***5a***

Sodium hydride (0.060 g, 60% in mineral oil) (1.5 mmol) washed with dry *n*-hexane three times was suspended in dry THF (5 mL). To this suspension the solution of **5a** (0.250 g, 1 mmol in 7 mL of dry THF) was added dropwise at 0 °C over a period of ca. 30 min. At this temperature the 1.5 mmol of the alkylating agent (benzylbromide or ethyl bromoacetate) was added to the resulted deep red mixture which was then allowed to warm up slowly to rt., stirred for 12 h and cooled down again to 0 °C. After the sequentional addition of cold MeOH (10 mL), brine (20 mL) and EtOAc (10 mL) the organic phase was separated, washed with brine (3 × 10 mL), dried over Na_2SO_4 and evaporated. The oily residue was crystallized by cyclohexane and the product was filtered off and dried. Yield: 0.145 g (44%) for **5e**; 0.218 g 0.153 g (45%) for **5f**. Within experimental error the analytical and spectroscopic data of **5e** were identical with those described in the previous section.

4.6.1. (S_p)-Ethyl 3-(4-oxoferroceno[d]pyridazin-4(3H)-yl)acetate (**5f**)

Brownish red powder. Mp.: 113–115 °C (decomp.); $[\alpha]_D^{25}$: +56.7° (DMSO); IR (cm^{-1}): 2983, 1749, 1665, 1447, 1348, 1198, 1029, 826, 758; ^{1}H NMR ($CDCl_3$): 8.10 (s, 1H, H1); 5.28 (d, ^2J = 14.8 Hz, 1H, NC$\underline{H}_A$H$_B$); 5.28 (br s, 1H, H5); 5.15 (d, ^2J = 16.0 Hz, 1H, NC$\underline{H}_A$H$_B$); 4.84 (br s, 1H, H7); 4.56 (d, ^2J = 16.0 Hz, 1H, NCH$_A\underline{H}_B$); 4.51 (br s, 1H, H6); 4.27 (qa, ^3J = 7.4 Hz, 2H, OC$\underline{H}_2$CH$_3$); 4.24 (s, 5H, η^5-$C_5\underline{H}_5$); 1.31 (t, ^3J = 7.4 Hz, 3H, OCH$_2$C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$): 169.0 ($\underline{C}O_2$Et); 166.5 (C4); 141.1 (C1); 78.8 (C7a); 74.2 (C6); 74.1 (C4a); 70.9 (η^5-$\underline{C}_5H_5$); 67.4 (C7); 66.4 (C5); 61.8 (O$\underline{C}H_2$CH$_3$); 51.8 (N$\underline{C}H_2$); 14.7 (OCH$_2\underline{C}$H$_3$); ^{15}N NMR ($CDCl_3$): 320 (N2); 179 (N3); Anal. Calcd. for $C_{16}H_{16}FeN_2O_3$ (340.15): C: 56.50; H: 4.74; N: 8.24; Found: C: 56.42; H: 4.69; N: 8.16%.

4.7. (2-Pyridylmethyl)ferroceno[d]pyridazin-4(3H)-one (***5g***)

Sodium hydride (0.120 g, 60% in mineral oil) (3 mmol) washed with dry *n*-hexane three times was suspended in dry THF (5 mL). To this suspension the solution of **5a** (0.250 g, 1 mmol in 7 mL of dry THF) was added dropwise at 0 °C over a period of ca. 30 min. At this temperature 2-bromomethylpyridine hydrobromide (0.385 g, 1.5 mmol) was added to the resulted deep red mixture which was then allowed to warm up slowly to rt., and stirred for 12 h. The workup of the reaction mixture described in Section 4.6 afforded the product as deep red powder. Yield: 0.221 g, (64%); mp.: 126–128 °C (decomp.); $[\alpha]_D^{25}$: +51.9° (DMSO); IR (cm^{-1}): 3091, 1661, 1591, 1435, 1345, 1335, 1108, 1028, 827, 752; ^{1}H NMR ($CDCl_3$): 8.62 (br s, 1H, H6′, py); 8.17 (s, 1H, H1); 7.68 (t, ^3J = 7.1 Hz, 1H, H4′, py); 7.39 (br s, 1H, H4′, py); 7.22 (br s, 1H, H3′, py); 5.64 (d, ^2J = 15.2 Hz, 1H, NC$\underline{H}_A$H$_B$); 5.32 (d, ^2J = 15.2 Hz, 1H, NCH$_A\underline{H}_B$); 5.29 (br s, 1H, H5); 4.85 (br s, 1H, H7); 4.51 (br s, 1H, H6); 4.14 (s, 5H, η^5-$C_5\underline{H}_5$); ^{13}C NMR ($CDCl_3$): 166.6 (C4); 157.5 (C2′, py); 149.6 (C6′, py); 141.3 (C1); 137.2 (C4′, py); 123.0 (C3′5′, two coalesced lines as evidenced by ^{1}H–^{13}C HSQC); 79.2 (C7a); 74.7 (C6); 74.0 (C4a); 67.3 (C7); 66.2 (C5); 70.6 (η^5-$\underline{C}_5H_5$); 55.5 (N$\underline{C}H_2$); ^{15}N NMR ($CDCl_3$): 328 (N1′, py); 321 (N2); 178 (N3); Anal. Calcd. for $C_{18}H_{15}FeN_3O$ (345.18): C: 62.63; H: 4.38; N: 12.17; Found: C: 62.57; H: 4.46; N: 12.14%.

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