Etorphine-Related Ferrocenyl-Substituted Morphinan Alkaloids

by **Gerhard Laus***[a]), **Johannes Schütz**[b]), **Herwig Schottenberger***[c]), **Max Andre**[d]), **Klaus Wurst**[c]), **Mariana Spetea**[b])[f]), **Karl-Hans Ongania**[e]), **Adrian G. Müller**[c]), and **Helmut Schmidhammer**[b])

[a]) *Immodal Pharmaka GmbH*, Bundesstrasse 44, A-6111 Volders
[b]) Institute of Pharmacy, Department of Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck
[c]) Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck
[d]) *Biochemie GmbH* (*Novartis Generics*), Biochemiestrasse 10, A-6250 Kundl
[e]) Institute of Organic Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck
[f]) Institute of Pharmacy, Department of Pharmacology and Toxicology, University of Innsbruck, Peter-Mayr-Strasse 1, A-6020 Innsbruck

The two diastereoisomeric ferrocenyl-substituted orvinols **2** and **3** were prepared. The modified alkaloids are still able to interact with opioid receptors (see *Table*). The ferrocene moiety allows highly selective and sensitive electrochemical detection. The X-ray crystal structure of the major isomer **2** was determined. The combination of a metallocene and a morphinan alkaloid holds promise for useful antitumor activity.

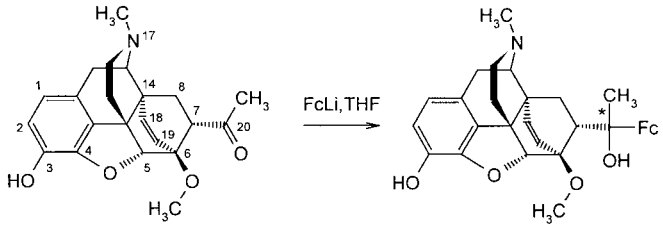
Introduction. – During recent years, bioorganometallic chemistry has evolved as a rapidly growing discipline [1] with potential applications in biomimetic [2] and enantioselective catalysis [3] and the development of new metal-based drugs. The antitumor activity of ferrocenium salts [4] and other iron sandwich compounds [5] has led to a combination of the anticancer agent cisplatin with the bio-oxidizable ferrocenyl (Fc) group [6]. The interactions of the antibiotic adriamycin with metallocene dichlorides have been studied in an effort to eliminate secondary toxic effects [7]. The antitumor activity of derivatives of titanocene dichloride has been assessed [8], and the interaction of other metallocene dihalides with biomolecular targets have been studied [9]. Radiolabeled β-ruthenocenylalanine has been evaluated as a potential pancreas-imaging agent [10]. New organometallic radiopharmaceuticals for the targeting of specific receptors and a ^{99m}Tc cyclopentadienide complex for use in diagnostic nuclear medicine have been reported [11]. Major advances in this field are the development of ferrocifen, a cytotoxic tamoxifen analogue [12], and of ferroquine, which is active against chloroquine-resistant malaria parasites [13]. Ferrocene reagents can be used for the derivatization in HPLC with electrochemical detection [14], and chiral ferrocene reagents were found to be suitable for the resolution of enantiomers [15]. Thus, organometallic tags are used for the detection of bioconjugates in complex mixtures, replacing the traditional radioactive labels [16], with ferrocenylethynylestradiol and ferrocenylethynylcholestadiene as recent examples [17]. Examples from the field of opioid alkaloids include π-complexes of morphine alkaloids with Fe, Mo, and Pd [18], and hexacarbonyldicobalt derivatives of ethynylcodeines [19].

It is known that opioid agonists inhibit breast-cancer-cell proliferation [20]. These cells possess only few δ and no μ sites, whereas κ-opioid receptors are the most widely expressed [21]. Etorphine (=(αR,5α,7α)-4,5-epoxy-3-hydroxy-6-methoxy-α,17-dimethyl-α-propyl-6,14-ethenomorphinan-7-methanol), a general opioid agonist that interacts with κ-opioid sites in human-breast-cancer cells, was shown to produce important changes in the cytoskeletal network of these cells [22]. It has also been suggested that radiolabeled probes for κ-opioid receptors may be useful in the diagnosis of brain neoplasms [23].

Therefore, it seemed to be of interest to envision new structures and to explore the potential of organometallic groups with possible cytotoxicity. The attachment of a metallocenyl group to an opioid vector (*e.g.*, etorphine analogue) may lead to a new class of compounds with antitumor properties and potential clinical relevance. In the present paper, synthesis, structural characterization, and biochemical evaluation of the two diastereoisomeric ferrocenyl-substituted orvinols **2** and **3**[1]) are described.

Results and Discussion. – *Synthesis.* The *Grignard* reaction with orvinones and thevinones has previously been shown to exhibit a remarkably high degree of stereoselectivity by asymmetric induction, and the products were obtained as almost pure diastereoisomers, although sometimes seriously competitive reduction was observed, whereas alkyllithiums were found to be less stereoselective [25]. Thus, addition of ferrocenyllithium [26] to orvinone (**1**) yielded in one step the two diastereoisomeric ferrocenylorvinols **2** and **3** (*Scheme*), which were readily separated by chromatography. The **2**-(20*S*) to **3**-(20*R*) ratio in the crude product mixture was determined as 57:43 by HPLC. No attempts were undertaken to optimize procedural details.

Scheme



1 **2** (*20S*)
3 (*20R*)

The ^{1}H-NMR spectra of **2** and **3** were in complete agreement with previous studies in the 6α,14α-ethenotetrahydrothebaine series. Accordingly, H–C(19) was assigned due to coupling with H–C(5), and the shift of H–C(5) at δ 4.5 was indicative of 7α substitution. In the diastereoisomeric methanols, the upfield shift of the olefinic protons H–C(18) and H–C(19) of **3** (δ 4.86, 5.18) as compared with those of **2** (δ 5.38, 5.92) and the downfield shift of H_α–C(8) of **3** (δ 0.92) as compared with that of **2** (δ 0.54) are possibly due to the shielding

[1]) The *IUPAC* numbering system for natural products and related compounds combined with arbitrary numbering was used for the morphinan alkaloids [24]; for systematic names, see *Exper. Part.*

and deshielding effects of the aromatic ferrocene moiety, in analogy to the diastereoisomeric phenylthevinols [27]. Thus, compound **2** could be tentatively assigned the (20*S*)-configuration[1]).

It was observed earlier that orvinols in acidic solutions eliminate H_2O to give the corresponding alkenes [28]. On monitoring the reaction by HPLC/MS, we found that dehydration of **2** is quite fast, even in 1 mM hydrochloric acid, but that also a slow re-addition of H_2O occurs, giving rise to the diastereoisomer **3** followed by further complex acid-catalyzed rearrangements.

X-Ray Structure Determinations. The crystal structures of two solvates of the major isomer **2**, with $CHCl_3$ and hexane, were determined. These solvates form isomorphic crystals with nearly equal lattice constants and the same alignment of the morphinan molecules. Values in brackets are for the hexane complex. The geometry of the new chiral center was confirmed. The cyclopentadienyl (Cp) rings are only slightly twisted, with a torsion angle of *ca.* 5° (*Fig. 1*). An intramolecular H-bond is observed between the 6-MeO group and the tertiary OH group with an O ··· O distance of 263.0 (261.1) pm. Intermolecular H-bonds form a chain in the direction of the *b*-axis by connecting the 3-OH group and the tertiary OH group with an O ··· O distance of 274.0 (272.3) pm. *Fig. 2* shows the packing along the *a*-axis with microchannels filled with the solvent $CHCl_3$. In both crystals, the solvents $CHCl_3$ and hexane occupy disordered positions in these channels.

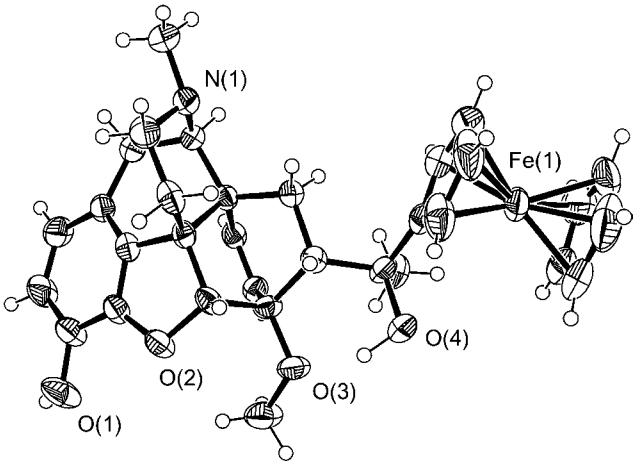


Fig. 1. *ORTEP View of* **2**-*(*20S*) drawn with 50% displacement ellipsoids.* The $CHCl_3$ molecule is not shown.

Opioid-Receptor Binding Studies. Opioid binding affinities of compounds **2**, **3**, and etorphine were determined in homogenates of rat brain (μ, δ) and guinea-pig brain (κ).The binding data expressed as inhibition-constant (K_i) values are shown in the *Table*. Both modified alkaloids bound with very high affinity (in the low-nanomolar range) to all three opioid receptors, although the interaction was approximately one order of magnitude weaker than that of etorphine at μ and κ receptors, and comparable at δ receptors (*Table*). Compound **2**, which has the same configuration as etorphine ((20*S*) of **2** corresponding to (20*R*) of the latter[1])), was slightly more active than the

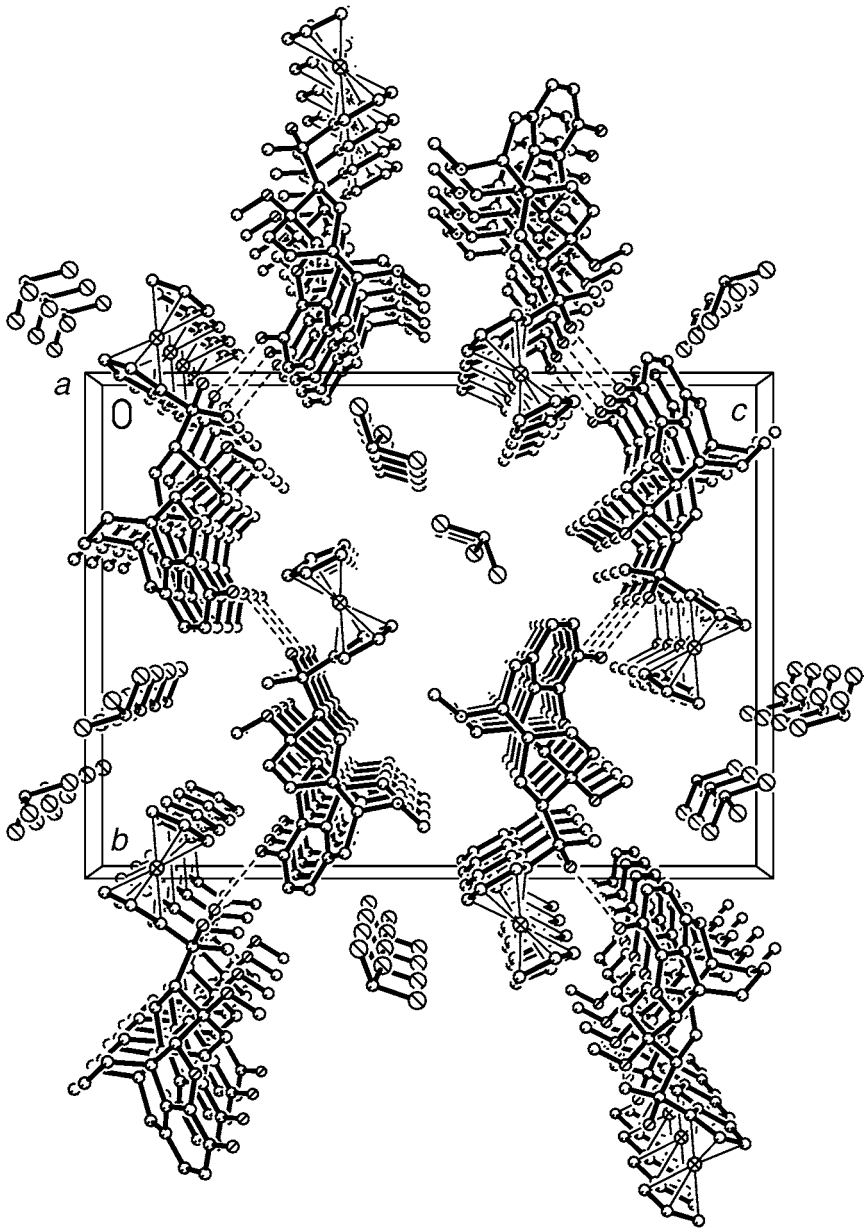


Fig. 2. *Intermolecular arrangement of* **2** *indicating H-bonding interactions*

diastereoisomer **3**. However, the selectivity profiles of compounds **2** and **3** were not significantly different from that of etorphine.

HPLC Tests. The Fc electrophore allows highly selective electrochemical detection with high sensitivity. Thus, the quantitation limit of compound **2** was 0.3 pmol and the

Table. *Opioid-Receptor Binding Affinities of Compounds* **2**, **3**, *and Etorphine Expressed as* K_i *Values* [nM][a])

	[^{3}H]DAMGO μ	[^{3}H]Ile^{5,6}deltorphin II δ	[^{3}H]U69,593 κ
2	1.22 ± 0.22	2.72 ± 0.47	1.84 ± 0.25
3	1.93 ± 0.21	4.20 ± 0.17	3.27 ± 0.02
Etorphine	0.27 ± 0.02	1.56 ± 0.29	0.78 ± 0.07

[a]) $\pm$ Standard error of the mean of triplicate measurements.

detection limit 0.1 pmol. In contrast, the quantitation limit was only 60 pmol and the detection limit 20 pmol when UV detection was used.

Conclusions and Outlook. – In this work, the first combination of a morphinan alkaloid with a transition-metal sandwich structure is reported. It will now be of interest to study the antiproliferative effects of the 'fecorphines' **2** and **3** on tumor cell lines. The attachment of substituted ferrocenes to give stabilized cations as well as the introduction of other metallocenes *via* different coupling techniques are targets of future research.

Experimental Part

General. HPLC: *LiChroCART cartridge* (125 × 4, *Merck*) packed with *LiChrospher 100 RP-18* (5 μm), thermostated at 25°; eluent MeCN/0.01M aq. phosphate buffer pH 7 60:40, flow 1.0 ml/min; *Merck-Hitachi L-4250* UV-VIS detector at 280 nm; t_R of **1** 2.0, ferrocene 6.8, **3** 7.2, and **2** 11.0 min. Electrochemical detection was performed with an *EG&G Princeton Applied Research 400* detector at +600 mV with a Ag/AgCl reference electrode. The limits of detection and quantitation were estimated from the residual standard deviation and the slope of regression lines of calibrations in these concentration ranges. IR Spectra: *Nicolet 510-FT-IR* and *Mattson Galaxy-FT-IR-3000* instruments; in cm^{-1}. NMR Spectra: *Varian Gemini-200* spectrometer; δ in ppm with Me_4Si as reference, *J* values in Hz. High-resolution (HR) MS: FAB with Cs gun and 3-nitrobenzyl alcohol matrix, *Finnigan-MAT-95* spectrometer.

X-Ray Structure Determination. Diffraction intensity data were collected by means of a *Nonius Kappa CCD* with graphite-monochromatized Mo-K_α radiation (λ 71.073 pm) and a nominal crystal to area detector distance of 36 mm. Intensities were integrated using DENZO and scaled with SCALEPACK. Several scans in the ϕ and ω direction were made to increase the number of redundant reflections, which were averaged in the refinement cycles. This procedure replaces an empirical absorption correction. The structures were solved with direct methods (SHELXS-86) and refined on F^2 (SHELXL-97). H-atoms at C-atoms were added geometrically and refined with a riding model. The H-atoms of the OH groups were found and refined with isotropic displacement parameters. All non-H-atoms were refined with anisotropic displacement parameters. Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication no. CCDC-208534 and -208535. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Opioid-Receptor Binding Studies. Rat and guinea-pig brain membranes for opioid-receptor binding assay were prepared as previously described [29]. Binding affinities to opioid receptors were determined by competitive binding assays with type-selective radioligands as previously described [29]. Inhibition constants (K_i, in nM) were calculated with the nonlinear least-square curve fitting by GraphPad Prism (version 3.0, San Diego, CA, USA) program. Etorphine was purchased from *Macfarlan Smith* (Edinburgh, United Kingdom).

(αS,5α,7α)- and (αR,5α,7α)-4,5-Epoxy-α-ferrocenyl-3-hydroxy-6-methoxy-α,17-dimethyl-6,14-ethenomorphinan-7-methanol (=*1-{(1S)- and (1R)-1-[(5α,7α)-4,5-Epoxy-3-hydroxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-yl]-1-hydroxyethyl}ferrocene*; **2** and **3**, resp.). A mixture of ferrocenyllithium (1.05 g, 5.47 mmol) and orvinone (=1-[(5α,7α)-4,5-epoxy-3-hydroxy-6-methoxy-17-methyl-6,14-ethenomorphinan-7-yl]ethanone;

1; 0.80 g, 2.18 mmol) prepared from oripavine by *Diels–Alder* reaction with but-1-en-3-one [30] under Ar was suspended in precooled (−60°) anh. THF, stirred at −50° for 10 min and at r.t. for 90 min, and then quenched with ice (10 g). The solvent was evaporated and the residue partitioned between sat. NH_4Cl soln. (200 ml) and CH_2Cl_2 (1 × 100 ml, 2 × 50 ml). The combined org. phase was washed with H_2O (2 × 100 ml) and brine (2 × 100 ml), dried (Na_2SO_4), and evaporated and the orange-brown foam (1.56 g) subjected to column chromatography (4 bar, silica gel *60*, CH_2Cl_2/MeOH/conc. NH_3 soln. 250 : 2 : 0.5 for the elution of **2** and 250 : 3 : 0.5 for **3**). The appropriate fractions were evaporated and the residues triturated each with light petroleum ether (1 ml). The resulting products were filtered off and dried: 0.16 g (13%) of **2** and 0.11 g (9%) of **3**, resp.

Data of **2**: M.p. 230–242° (dec., after a phase transition at 223°). IR (KBr): 3448, 3382, 3095, 2927, 2840, 2796, 1637, 1608, 1502, 1467, 1373, 1317, 1122, 1018, 819. ^{1}H-NMR ($CDCl_3$): 6.58 (*d*, ^3J = 8.0, H−C(1)); 6.44 (*d*, ^3J = 8.0, H−C(2)); 5.92 (*dd*, ^3J = 9.2, ^4J = 0.6, H−C(19)); 5.38 (*d*, ^3J = 9.2, H−C(18)); 5.04 (*s*, OH); 4.52 (*d*, ^4J = 0.6, H−C(5)); 4.27 (*m*, 1 H(Cp)); 4.21 (*s*, 5 H(Cp)); 4.14 (*m*, 1 H(Cp)); 4.03 (*m*, 1 H(Cp)); 3.87 (*m*, 1 H(Cp)); 3.77 (*s*, MeO); 2.23 (*s*, MeN); 1.33 (*s*, Me−C−C(7)); 0.54 (*dd*, ^3J = 8.0, ^2J = 13.2, H_α−C(8)). ^{13}C-NMR ($CDCl_3$): 146.5; 137.3; 135.5; 134.2; 127.9; 124.5; 119;6; 116.1; 99.0; 97.7; 84.0; 74.2; 68.6; 67.7; 66.5; 65.7; 59.8; 55.0; 50.0; 47.4; 45.3; 43.4; 42.9; 33.2; 31.1; 23.9; 22.3. HR-FAB-MS: 554.1958 ($C_{32}H_{36}FeNO_4^+$, $[M+H]^+$; calc. 554.1988).

Crystal Data of **2**·$CHCl_3$: Yellow prism (0.35 × 0.2 × 0.08 mm) from $CHCl_3$, $C_{32}H_{35}FeNO_4 \cdot CHCl_3$, *M* 672.8, orthorhombic, a = 672.59(1), b = 1869.07(4), c = 2540.39(6) pm, $\alpha = \beta = \gamma = 90°$, V = 3.1936(1) nm^3, *T* 293 K, space group $P2_12_12_1$, Z = 4, μ = 0.761 mm^{-1}, *Flack* parameter $x = -0.001(18)$, 15187 reflections measured, 4450 independent (R_{int} = 0.0331), 4049 observed, R_1 = 0.0372 and wR_2 = 0.0954 ($I > 2\sigma(I)$), R_1 = 0.0433 and wR_2 = 0.0988 (all data).

Crystal Data of **2**·*hexane:* Yellow prism (0.4 × 0.3 × 0.2 mm) from hexane extract of the crude product mixture, $C_{32}H_{35}FeNO_4 \cdot C_6H_{14}$, *M* 639.6, orthorhombic, a = 672.05(2), b = 1853.38(7), c = 2562.5(1) pm, $\alpha = \beta = \gamma = 90°$, V = 3.1918(2) nm^3, *T* 228 K, space group $P2_12_12_1$, Z = 4, μ = 0.515 mm^{-1}, *Flack* parameter x = 0.01(2), 12357 reflections measured, 3408 independent (R_{int} = 0.0372), 3154 observed, R_1 = 0.0379 and wR_2 = 0.0936 ($I > 2\sigma(I)$), R_1 = 0.0425 and wR_2 = 0.0966 (all data).

Data of **3**: M.p. 245–250° (dec., after phase transitions at 120°, 140°, and 210°). IR (KBr): 3413, 3244, 3105, 2952, 2923, 2900, 2836, 2796, 2765, 1630, 1607, 1497, 1106, 1023, 816. ^{1}H-NMR ($CDCl_3$): 6.52 (*d*, ^3J = 8.0, H−C(1)); 6.38 (*d*, ^3J = 8.0, H−C(2)); 5.30 (*s*, OH); 5.18 (*d*, ^3J = 8.8, H−C(19)); 4.86 (*d*, ^3J = 8.8, H−C(18)); 4.50 (*s*, H−C(5)); 4.17 ('*s*', 6 H(Cp)); 4.02 (*m*, 1 H(Cp)); 3.97 (*m*, 1 H(Cp)); 3.84 (*m*, 1 H(Cp)); 3.67 (*s*, MeO); 2.35 (*s*, MeN); 1.47 (*s*, Me−C−C(7)); 0.92 (*dd*, ^3J = 7.3, ^2J = 12.5, H_α−C(8)). ^{13}C-NMR ($CDCl_3$): 146.6; 137.4; 134.0; 132.7; 127.7; 123.8; 119.6; 116.1; 99.3; 95.2; 84.0; 74.5; 68.5; 68.2; 67.1; 66.9; 66.5; 60.0; 54.7; 49.9; 46.9; 45.6; 43.5; 42.4; 33.2; 29.6; 28.2; 22.2. HR-FAB-MS: 554.1995 ($C_{32}H_{36}FeNO_4^+$, $[M+H]^+$; calc. 554.1988).

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