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Ferrocene compounds
Part XXXIII. Synthesis and characterization of amino acids containing skeletal 1,1′-ferrocenylene unit☆

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Abstract

The syntheses of 1′-(3-aminopropyl)ferrocene-1-carboxylic acid (**7**), 1′-amino-1-ferrocenebutyric acid (**14**) and their derivatives are reported. Reactions of 1′-methoxycarbonyl-1-ferrocenebutyric acid (**3**) or methyl 1′-carboxy-1-ferrocenebutyrate (**10**) with ethyl chloroformate/triethylamine/sodium azide gave methyl 1′-(3-azidocarbonylpropyl)ferrocene-1-carboxylate (**4**) and methyl 1′-azidocarbonyl-1-ferrocenebutyrate (**11**). These azides were rearranged by heating in acetic anhydride and hydrolyzed into *N*-acetyl derivatives of **7** and **14**. The crucial intermediates **4** and **11** were transformed by the action of *t*-BuOH into Boc-**7** and Boc-**14**. The crystal and molecular structures of the intermediates methyl 1′-(3-acetamidopropyl)ferrocene-1-carboxylate (**5**) and *tert*-butyl 1′-(3-methoxycarbonylpropyl)-1-ferrocenecarbamate (**15**) have been determined by the single crystal X-ray analysis. Compound **5** crystallizes in two polymorphic forms (**5a** and **5b**); one of them (**5b**) contains two crystallographically independent molecules. The molecules **5a** and **5b** differentiate only in the conformation of $(CH_2)_3NHAc$ part of the molecules exhibiting conformational polymorphism. The crystal structure is dominated by the intermolecular hydrogens bonds of N–H···O type (2.820(1)–2.840(2) Å) linking molecules into endless chains in all three structures. The chains are further interconnected by the C–H···O hydrogen bonds (3.483(1)–3.267(2) Å) in **5a** and **15**, but not in **5b**.The structural features of **5** and **15** determined by the single crystal X-ray analysis, reveal existence of intermolecular hydrogens bonds of N–H···O type (2.820(1)–2.840(2) Å).

Keywords: Ferrocene; Unnatural amino acids; Bioorganometallic chemistry; X-ray single crystal analysis; Conformational polymorphism

1. Introduction

Bioorganometallic chemistry is a recent propulsive discipline dealing with organometallic compounds coupled with biomolecules. Here, conjugates of metallocenes with amino acids or peptides are of greatest interest [2,3]. Numerous *C*- and *N*-ferrocenyl substituted α-amino acids were prepared. 1,1′-Ferrocenylene-bisalanine and resolved β-ferrocenylalanine were described recently [4]. π-Electron system of aromatic α-amino acids is a target for the introduction of transition metal complex fragments forming the metallocene moieties: in such a way syntheses of metallocenyl-substituted alanines, tryptophanes, and tyrosines were done [5].

The organometallic amino acids described can be incorporated into peptide systems providing new biomaterials, reversible masked peptides, or efficient redox systems. Racemic or resolved β-ferrocenylalanine and other ferrocene-containing amino acids were used to prepare organometallic derivatives of prolyl-, glycyl-, tyrosyl-, and leucyl-containing peptides [6,7].

Syntheses, crystal structures, and electrochemical properties of a number of ferrocene systems bearing oligopeptide and podand dipeptide chains were investi-

☆ For Part XXXII, see [1].

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gated [8,9]. The particular stability of ferrocenylalanine allowed even solid-phase peptide syntheses to be carried out [3]. Chemical models of protein β-sheets and α-helices based on hydrogen-bonding capability of peptide chains are studied by using ferrocene template scaffolds. Such molecules could serve as models for chemical recognition of natural products (proteins, DNA) [10,11].

During our studies on ferrocene-containing oligoamides **I** ($m = 0$–3, $n = 4$–6,) we have prepared the corresponding monomers—heteroannularly substituted amino amido acids **I** ($m = 2$ and 3, $n = 1$) presented on Fig. 1—by reactions of 1,1-(1,1′-ferrocenylene)bis(ethylamine) with either succinic or glutaric anhydride in toluene. The spectral properties and solubility of these compounds indicated their Zwitterionic character [12].

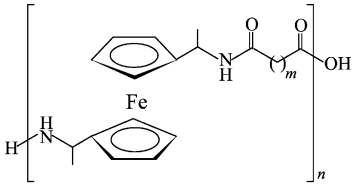
Two types of similar amino acids with "inserted" ferrocene units are homo- **II** and heteroannularly substituted compounds **III** presented on Fig. 2.

N,*N*-Dimethyl derivative of **II** ($m = 0$, $n = 1$) was prepared by regioselective lithiation and carboxylation of *N*,*N*-dimethyl(ferrocenylmethyl)amine [13]. Hydrogenation of (*R*)- and (*S*)-methyl 2-nitroferrocene-1-carboxylate gave the corresponding amino ester but the attempt to obtain the parent amino acid **II** (m, $n = 0$) by its hydrolysis resulted in decomposition [14].

In our recent publication [15] efficient syntheses of 1′-aminoferrocene-1-carboxylic acid [16] and its *C*- and *N*-protected derivatives are described. Here, we will report our findings on preparation and structural characterization of two higher homologues of this type of amino acids, having in mind their conversion into the corresponding oligopeptides, as well as a study of their metal chelates [17].

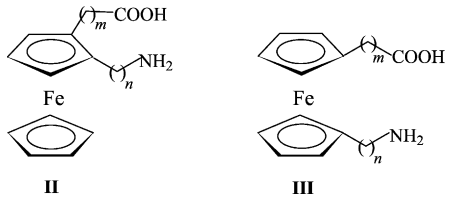
2. Results and discussion

Our current experiments for the first time demonstrated possibility of preparation of oligopeptides **IV** containing *nonterminal* ferrocene amino acids. Using appropriately protected compound **III** (m, $n = 0$) and natural amino acids (Gly, Ala, Leu,...) and/or dipeptides (Ala-Ala, Ala-Gly,...) these oligopeptides (m, $n = 0$; R = H, Me; p, $r = 0$, 1, 2) were synthesized in solution by DCC/HOBt protocol in good yields. On the basis of the spectral analysis it is obvious that these oligopeptides existed in diluted solutions as a species containing 1–3 intramolecular hydrogen bonds presenting in such a way models for antiparallel β-sheet conformation [18] (Fig. 3).



I, $m = 0$-3; $n = 1$-6;

Fig. 1.



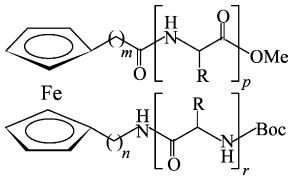
II **III**

Fig. 2.

Prompted by these results we decided to prepare higher homologues of type **III** ($m = 0$, $n = 3$; $m = 3$, $n = 0$) planning studies of their coupling into the corresponding oligomers by the above mentioned methods. Having in mind hydrogen-bonding ability of peptide strands one could expect difference in organization of "rigid" peptides derived from **III** (m, $n = 0$) and of their homologues with flexible trimethylene spacer between ferrocene scaffold and NH or CO. Obviously, parallel structural studies of these compounds will be of greatest interest.

In the first attempt to prepare 1′-(3-aminopropyl)ferrocene-1-carboxylic acid (**7**) and 1′-amino-1-ferrocenebutyric acid (**14**) we started from methyl ferrocenecarboxylate (**1**) (which was obtained in high overall yield by oxidation of *N*,*N*-diphenylferrocenecarboxyamide into ferrocenecarboxylic acid [19] and its conversion into the corresponding ester [20]). This ester was converted with succinic anhydride in the presence of $AlCl_3$ into ester-keto acid **2**, which was reduced into ester-acid **3**. By action of ethyl chloroformate and triethylamine ester-acid **3** was converted into the mixed anhydride, which gave 99% of methyl 1′-(3-azidocarbonylpropyl)ferrocene-1-carboxylate (**4**) by adding of an aqueous solution of sodium azide (under the conditions for preparation of ferrocenecarbazide [17]). Azide-ester **4** was rearranged and acylated by heating in acetic anhydride giving methyl 1′-(3-acetamidopropyl)ferrocene-1-carboxylate (**5**) in 63% yield.

The crystal structure analysis of single crystal samples of compound **5** reveals two crystal modifications, one of them containing two crystallographically independent molecules within asymmetric unit ($Z' = 1$ (**5a**) and $Z' = 2$ (**5b**) for monoclinic $P2_1/c$ space group) (Figs. 4 and 5).



IV

Fig. 3.

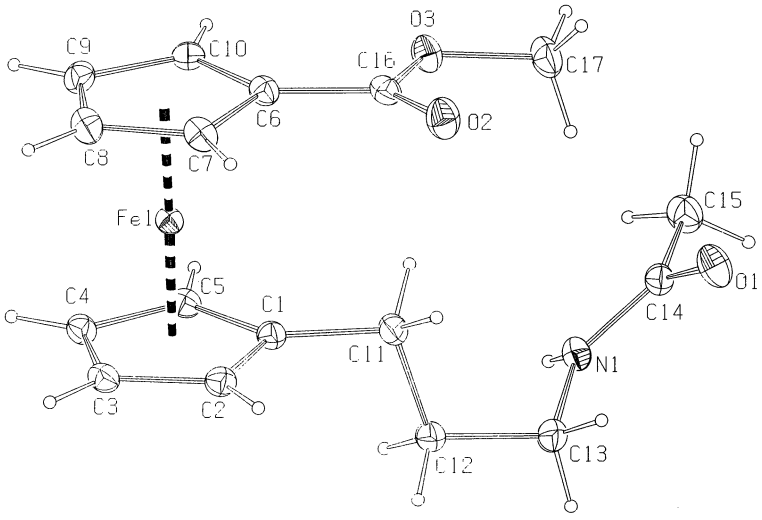


Fig. 4. An ORTEP view of the red–orange prismatic modification of the polymorph **5a** at 100 K showing atom numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

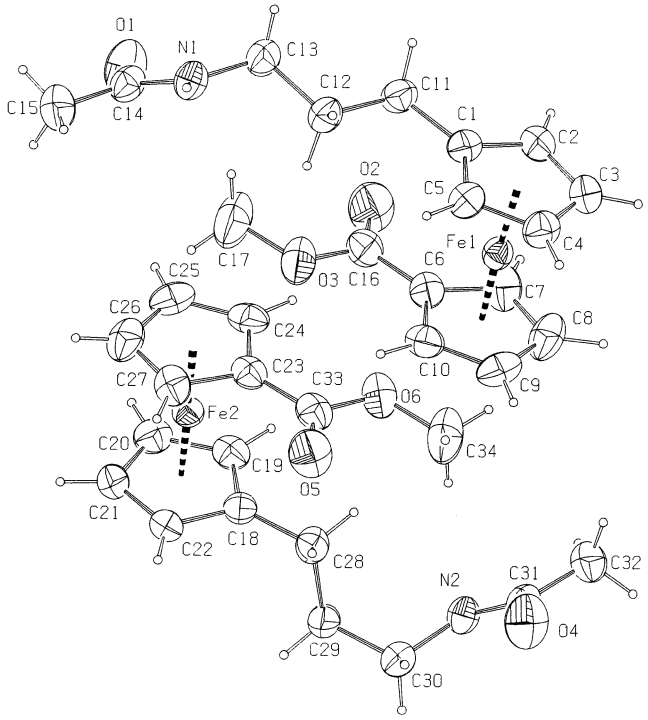


Fig. 5. An ORTEP view of the two independent molecules of the red–orange irregular modification of the polymorph **5b** at 297 K showing atom numbering scheme. The conformation of one of the two molecules (containing Fe2) is almost the same as of **5a**. Displacement ellipsoids are drawn at the 50% probability level.

These two modifications exhibit conformational polymorphism with the greatest difference in the $(CH_2)_3NHAc$ moiety conformation. The twisting around C12–C13 single bond of the spacer is described by the C11–C12–C13–N1 torsion angles values which are almost the same in **5a** polymorphic form and in one of the molecules in **5b** amounting −66.4(1)° (for the C11–C12–C13–N1 torsion angle in **5a**) and −65.2(2)° (for the torsion angle C28–C29–C30–N2 in **5b**). On the other hand, the C11–C12–C13–N1 torsion angle in **5b** is 174.6(2)°.

This compound, containing trimethylene spacer between acetamido group and cyclopentadiene ring, is a homologue of methyl 1′-acetamidoferrocene-1-carboxylate [15,21].

In the structure of red–orange prismatic modification **5a** the shortest and the longest Fe–C bond distances are Fe1–C6 and Fe1–C8 (2.038(1) and 2.065(1) Å) indicating that there is no difference between Fe–C (unsubstituted) and Fe–C (substituted) bond distances (Table 1). The cyclopentadienyl (Cp) rings are almost in the fully eclipsed conformation (the dihedral angle between two planes calculated through ring atoms C1–C5 and C6–C10 is 0.89(7)°). The distances between the Fe atoms and the centroids of the Cp rings are Fe1–Cg1 (C1–C5) 1.6577(5) and Fe1–Cg2 (C6–C10) 1.6504(5) Å, and the angle is Cg1–Fe1–Cg2 178.83(1)°.

In the structure of red–orange irregular block polymorphic modification **5b** the ferrocenyl moieties geometry is similar to **5a**. The shortest Fe–C bond distance in both molecules is Fe2–C23 being of 2.037(2) Å and the longest one amounts 2.084(2) Å (for Fe1–C1) (Table 1). The deviation from fully eclipsed conformation of Cp rings is not significant being 3.34(13)° calculated between C1–C5 and C6–C10 Cp rings and 1.05(12)° calculated between C18–C22 and C23–C27 Cp rings of another molecule. The distances between the Fe atoms and the centroids of the Cp rings are Fe1–Cg1 (C1–C5) 1.6610(9), Fe1–Cg2 (C6–C10) 1.6553(10), Fe2–Cg3 (C18–C229 1.6541(9) and Fe2–Cg4 (C23–C27) 1.6492(10) Å. The corresponding angles are Cg1–Fe1–Cg2 and Cg3–Fe2–Cg4 177.08(2) and 178.77(2)°, respectively.

Table 1
Relevant bond distances (Å) and bond angles (°) for the structures **5a**, **5b** and **15**

5a			
Bond distances			
Fe(1)–C(1)	2.0628(9)	C(1)–C(5)	1.4311(13)
Fe(1)–C(2)	2.0587(10)	C(1)–C(2)	1.4327(13)
Fe(1)–C(3)	2.0505(10)	C(1)–C(11)	1.4986(13)
Fe(1)–C(4)	2.0504(10)	C(2)–C(3)	1.4298(14)
Fe(1)–C(5)	2.0553(9)	C(3)–C(4)	1.4268(14)
Fe(1)–C(6)	2.0381(10)	C(4)–C(5)	1.4245(14)
Fe(1)–C(9)	2.0579(10)	C(6)–C(7)	1.4337(13)
Fe(1)–C(7)	2.0504(10)	C(6)–C(10)	1.4388(14)
Fe(1)–C(10)	2.0398(10)	C(6)–C(16)	1.4655(14)
Fe(1)–C(8)	2.0646(10)	C(7)–C(8)	1.4241(15)
O(1)–C(14)	1.2428(13)	C(8)–C(9)	1.4276(15)
O(2)–C(16)	1.2115(13)	C(9)–C(10)	1.4252(14)
O(3)–C(16)	1.3516(12)	C(11)–C(12)	1.5316(14)
O(3)–C(17)	1.4461(13)	C(12)–C(13)	1.5216(14)
N(1)–C(14)	1.3350(13)	C(14)–C(15)	1.5074(15)
N(1)–C(13)	1.4616(14)		
Bond angles			
C(6)–Fe(1)–C(4)	162.79(4)	C(14)–N(1)–C(13)	123.12(9)
C(10)–Fe(1)–C(4)	124.42(4)	C(5)–C(1)–C(2)	107.40(8)
C(7)–Fe(1)–C(4)	154.22(4)	C(5)–C(1)–C(11)	125.89(9)
C(6)–Fe(1)–C(3)	155.49(4)	C(2)–C(1)–C(11)	126.52(9)
C(10)–Fe(1)–C(3)	161.69(4)	C(3)–C(2)–C(1)	108.02(8)
C(7)–Fe(1)–C(3)	120.04(4)	C(4)–C(3)–C(2)	108.21(9)
C(6)–Fe(1)–C(5)	126.18(4)	C(5)–C(4)–C(3)	107.75(9)
C(10)–Fe(1)–C(5)	107.24(4)	C(4)–C(5)–C(1)	108.61(8)
C(7)–Fe(1)–C(5)	164.05(4)	C(7)–C(6)–C(10)	107.89(9)
C(4)–Fe(1)–C(9)	106.56(4)	C(7)–C(6)–C(16)	123.06(9)
C(3)–Fe(1)–C(9)	124.77(4)	C(10)–C(6)–C(16)	128.98(9)
C(5)–Fe(1)–C(9)	119.74(4)	C(8)–C(7)–C(6)	108.00(9)
C(6)–Fe(1)–C(2)	120.93(4)	C(7)–C(8)–C(9)	108.07(9)
C(10)–Fe(1)–C(2)	155.88(4)	C(10)–C(9)–C(8)	108.53(9)
C(7)–Fe(1)–C(2)	108.28(4)	C(9)–C(10)–C(6)	107.51(9)
C(9)–Fe(1)–C(2)	162.46(4)	C(1)–C(11)–C(12)	110.12(8)
C(6)–Fe(1)–C(1)	108.28(4)	C(13)–C(12)–C(11)	113.90(9)
C(10)–Fe(1)–C(1)	120.41(4)	N(1)–C(13)–C(12)	112.83(8)
C(7)–Fe(1)–C(1)	126.66(4)	O(1)–C(14)–N(1)	122.68(10)
C(9)–Fe(1)–C(1)	154.96(4)	O(1)–C(14)–C(15)	120.98(9)
C(4)–Fe(1)–C(8)	119.24(4)	N(1)–C(14)–C(15)	116.32(9)
C(3)–Fe(1)–C(8)	107.19(4)	O(2)–C(16)–O(3)	123.10(9)
C(5)–Fe(1)–C(8)	154.16(4)	O(2)–C(16)–C(6)	124.41(9)
C(16)–O(3)–C(17)	115.29(8)	O(3)–C(16)–C(6)	112.48(8)
5b			
Bond distances			
Fe(1)–C(1)	2.0843(18)	N(2)–C(30)	1.455(3)
Fe(1)–C(2)	2.050(2)	C(1)–C(2)	1.420(3)
Fe(1)–C(3)	2.039(2)	C(1)–C(5)	1.423(3)
Fe(1)–C(4)	2.042(2)	C(1)–C(11)	1.501(3)
Fe(1)–C(5)	2.0536(19)	C(2)–C(3)	1.418(3)
Fe(1)–C(6)	2.0433(19)	C(3)–C(4)	1.421(3)
Fe(1)–C(7)	2.045(2)	C(4)–C(5)	1.420(3)
Fe(1)–C(8)	2.063(2)	C(6)–C(7)	1.430(3)
Fe(1)–C(9)	2.051(2)	C(6)–C(10)	1.433(3)
Fe(1)–C(10)	2.045(2)	C(6)–C(16)	1.457(3)
Fe(2)–C(18)	2.0623(17)	C(7)–C(8)	1.409(3)
Fe(2)–C(19)	2.0494(17)	C(8)–C(9)	1.412(3)
Fe(2)–C(20)	2.042(2)	C(9)–C(10)	1.419(3)
Fe(2)–C(21)	2.040(2)	C(11)–C(12)	1.513(3)
Fe(2)–C(22)	2.0485(19)	C(12)–C(13)	1.519(3)
Fe(2)–C(23)	2.0368(18)	C(14)–C(15)	1.499(3)
Fe(2)–C(24)	2.038(2)	C(18)–C(19)	1.429(3)

Table 1 (*Continued*)

5b			
Bond distances			
Fe(2)–C(25)	2.047(2)	C(18)–C(22)	1.423(3)
Fe(2)–C(26)	2.054(2)	C(18)–C(28)	1.493(3)
Fe(2)–C(27)	2.0418(19)	C(19)–C(20)	1.418(3)
O(1)–C(14)	1.234(2)	C(20)–C(21)	1.416(3)
O(2)–C(16)	1.205(3)	C(21)–C(22)	1.417(3)
O(3)–C(16)	1.346(3)	C(23)–C(27)	1.424(3)
O(3)–C(17)	1.444(3)	C(23)–C(24)	1.433(3)
O(4)–C(31)	1.237(2)	C(23)–C(33)	1.463(3)
O(5)–C(33)	1.203(2)	C(24)–C(25)	1.414(3)
O(6)–C(33)	1.346(2)	C(25)–C(26)	1.412(3)
O(6)–C(34)	1.448(3)	C(26)–C(27)	1.409(3)
N(1)–C(14)	1.323(2)	C(28)–C(29)	1.525(3)
N(1)–C(13)	1.448(3)	C(29)–C(30)	1.517(3)
N(2)–C(31)	1.321(2)	C(31)–C(32)	1.499(3)
Bond angles			
C(3)–Fe(1)–C(6)	156.77(9)	C(7)–C(8)–C(9)	108.20(19)
C(4)–Fe(1)–C(6)	162.09(8)	C(8)–C(9)–C(10)	108.5(2)
C(3)–Fe(1)–C(7)	119.83(9)	C(9)–C(10)–C(6)	107.68(18)
C(4)–Fe(1)–C(7)	154.37(9)	C(1)–C(11)–C(12)	114.57(16)
C(3)–Fe(1)–C(10)	159.14(9)	C(11)–C(12)–C(13)	112.31(17)
C(4)–Fe(1)–C(10)	123.79(9)	N(1)–C(13)–C(12)	111.52(17)
C(6)–Fe(1)–C(2)	123.15(8)	O(1)–C(14)–N(1)	121.9(2)
C(7)–Fe(1)–C(2)	108.18(10)	O(1)–C(14)–C(15)	121.7(2)
C(10)–Fe(1)–C(2)	159.43(9)	N(1)–C(14)–C(15)	116.48(19)
C(3)–Fe(1)–C(9)	121.76(9)	O(2)–C(16)–O(3)	123.4(2)
C(4)–Fe(1)–C(9)	105.87(9)	O(2)–C(16)–C(6)	124.5(2)
C(2)–Fe(1)–C(9)	158.80(9)	O(3)–C(16)–C(6)	112.08(18)
C(6)–Fe(1)–C(5)	126.82(8)	C(22)–C(18)–C(19)	106.99(16)
C(7)–Fe(1)–C(5)	163.66(9)	C(22)–C(18)–C(28)	126.35(18)
C(10)–Fe(1)–C(5)	109.28(8)	C(19)–C(18)–C(28)	126.54(17)
C(9)–Fe(1)–C(5)	121.79(9)	C(20)–C(19)–C(18)	108.52(17)
C(3)–Fe(1)–C(8)	105.22(9)	C(21)–C(20)–C(19)	107.79(18)
C(4)–Fe(1)–C(8)	119.11(9)	C(20)–C(21)–C(22)	108.21(18)
C(2)–Fe(1)–C(8)	123.44(10)	C(21)–C(22)–C(18)	108.48(18)
C(5)–Fe(1)–C(8)	155.49(9)	C(27)–C(23)–C(24)	107.46(18)
C(6)–Fe(1)–C(1)	110.68(8)	C(27)–C(23)–C(33)	123.93(18)
C(7)–Fe(1)–C(1)	126.63(9)	C(24)–C(23)–C(33)	128.57(18)
C(10)–Fe(1)–C(1)	124.44(8)	C(25)–C(24)–C(23)	107.44(19)
C(9)–Fe(1)–C(1)	158.43(9)	C(26)–C(25)–C(24)	108.7(2)
C(8)–Fe(1)–C(1)	161.15(9)	C(26)–C(27)–C(23)	108.29(19)
C(23)–Fe(2)–C(21)	155.89(8)	C(18)–C(28)–C(29)	111.19(16)
C(24)–Fe(2)–C(21)	161.11(9)	C(30)–C(29)–C(28)	113.49(18)
C(23)–Fe(2)–C(20)	162.59(8)	N(2)–C(30)–C(29)	112.53(17)
C(24)–Fe(2)–C(20)	124.49(9)	O(4)–C(31)–N(2)	122.04(19)
C(21)–Fe(2)–C(27)	120.25(9)	O(4)–C(31)–C(32)	121.44(19)
C(20)–Fe(2)–C(27)	154.59(8)	N(2)–C(31)–C(32)	116.51(18)
C(21)–Fe(2)–C(25)	124.24(9)	O(5)–C(33)–O(6)	122.9(2)
C(20)–Fe(2)–C(25)	106.91(9)	O(5)–C(33)–C(23)	124.54(19)
C(23)–Fe(2)–C(22)	121.51(8)	O(6)–C(33)–C(23)	112.58(17)
C(24)–Fe(2)–C(22)	156.94(8)	C(25)–Fe(2)–C(18)	156.32(9)
C(27)–Fe(2)–C(22)	108.24(9)	C(26)–Fe(2)–C(18)	162.42(9)
C(25)–Fe(2)–C(22)	161.39(9)	C(14)–N(1)–C(13)	123.30(18)
C(23)–Fe(2)–C(19)	126.22(8)	C(31)–N(2)–C(30)	123.71(18)
C(24)–Fe(2)–C(19)	108.02(8)	C(2)–C(1)–C(5)	107.26(17)
C(27)–Fe(2)–C(19)	163.60(8)	C(2)–C(1)–C(11)	125.28(17)
C(25)–Fe(2)–C(19)	120.81(9)	C(5)–C(1)–C(11)	127.33(17)
C(21)–Fe(2)–C(26)	106.97(9)	C(3)–C(2)–C(1)	108.61(18)
C(20)–Fe(2)–C(26)	119.71(9)	C(2)–C(3)–C(4)	107.87(18)
C(22)–Fe(2)–C(26)	125.12(9)	C(5)–C(4)–C(3)	107.75(18)
C(19)–Fe(2)–C(26)	155.02(9)	C(4)–C(5)–C(1)	108.49(18)
C(23)–Fe(2)–C(18)	108.63(7)	C(7)–C(6)–C(10)	107.13(18)
C(24)–Fe(2)–C(18)	121.62(8)	C(7)–C(6)–C(16)	124.08(18)

Table 1 (*Continued*)

Bond angles			
C(27)–Fe(2)–C(18)	126.20(8)	C(10)–C(6)–C(16)	128.78(18)
C(8)–C(7)–C(6)	108.44(19)		
15			
Bond angles			
Fe(1)–C(1)	2.0576(14)	C(1)–C(5)	1.431(2)
Fe(1)–C(2)	2.0439(14)	C(1)–C(2)	1.4320(19)
Fe(1)–C(3)	2.0472(14)	C(1)–C(11)	1.499(2)
Fe(1)–C(4)	2.0504(14)	C(2)–C(3)	1.426(2)
Fe(1)–C(5)	2.0503(13)	C(3)–C(4)	1.431(2)
Fe(1)–C(6)	2.0679(13)	C(4)–C(5)	1.433(2)
Fe(1)–C(7)	2.0509(13)	C(6)–C(7)	1.4270(18)
Fe(1)–C(8)	2.0437(14)	C(6)–C(10)	1.4297(19)
Fe(1)–C(9)	2.0463(14)	C(7)–C(8)	1.428(2)
Fe(1)–C(10)	2.0636(14)	C(8)–C(9)	1.426(2)
O(1)–C(14)	1.193(2)	C(9)–C(10)	1.4297(19)
O(2)–C(14)	1.336(2)	C(11)–C(12)	1.535(2)
O(2)–C(15)	1.448(2)	C(12)–C(13)	1.528(2)
O(3)–C(16)	1.2197(16)	C(13)–C(14)	1.505(2)
O(4)–C(16)	1.3499(16)	C(17)–C(18)	1.521(2)
O(4)–C(17)	1.4745(17)	C(17)–C(19)	1.522(2)
N(1)–C(16)	1.3513(17)	C(17)–C(20)	1.524(2)
N(1)–C(6)	1.4049(17)		
Bond angles			
C(8)–Fe(1)–C(2)	121.63(6)	C(5)–C(1)–C(11)	126.72(13)
C(2)–Fe(1)–C(9)	158.17(6)	C(2)–C(1)–C(11)	125.89(13)
C(8)–Fe(1)–C(3)	106.65(6)	C(3)–C(2)–C(1)	108.60(12)
C(9)–Fe(1)–C(3)	122.50(6)	C(2)–C(3)–C(4)	107.95(12)
C(8)–Fe(1)–C(5)	159.76(6)	C(3)–C(4)–C(5)	107.68(12)
C(9)–Fe(1)–C(5)	123.83(6)	C(1)–C(5)–C(4)	108.47(12)
C(8)–Fe(1)–C(4)	122.82(6)	N(1)–C(6)–C(7)	121.83(12)
C(9)–Fe(1)–C(4)	107.80(6)	N(1)–C(6)–C(10)	129.33(12)
C(2)–Fe(1)–C(7)	106.31(6)	C(7)–C(6)–C(10)	108.70(12)
C(3)–Fe(1)–C(7)	121.94(6)	C(6)–C(7)–C(8)	107.53(12)
C(5)–Fe(1)–C(7)	158.43(6)	C(9)–C(8)–C(7)	108.15(12)
C(4)–Fe(1)–C(7)	158.69(6)	C(8)–C(9)–C(10)	108.35(12)
C(8)–Fe(1)–C(1)	157.77(6)	C(6)–C(10)–C(9)	107.26(12)
C(9)–Fe(1)–C(1)	159.85(6)	C(1)–C(11)–C(12)	111.13(12)
C(7)–Fe(1)–C(1)	121.75(6)	C(13)–C(12)–C(11)	112.20(12)
C(2)–Fe(1)–C(10)	159.18(6)	C(14)–C(13)–C(12)	113.43(13)
C(3)–Fe(1)–C(10)	159.04(6)	O(1)–C(14)–O(2)	123.05(17)
C(5)–Fe(1)–C(10)	108.25(6)	O(1)–C(14)–C(13)	125.19(18)
C(4)–Fe(1)–C(10)	123.24(6)	O(2)–C(14)–C(13)	111.76(15)
C(1)–Fe(1)–C(10)	123.28(6)	O(3)–C(16)–O(4)	125.27(12)
C(2)–Fe(1)–C(6)	122.79(6)	O(3)–C(16)–N(1)	125.45(13)
C(3)–Fe(1)–C(6)	158.53(6)	O(4)–C(16)–N(1)	109.28(11)
C(5)–Fe(1)–C(6)	123.36(5)	O(4)–C(17)–C(18)	109.82(12)
C(4)–Fe(1)–C(6)	159.44(6)	O(4)–C(17)–C(19)	101.80(12)
C(1)–Fe(1)–C(6)	107.65(5)	C(18)–C(17)–C(19)	110.82(14)
C(14)–O(2)–C(15)	116.17(17)	O(4)–C(17)–C(20)	110.94(12)
C(16)–O(4)–C(17)	120.34(11)	C(18)–C(17)–C(20)	112.42(14)
C(16)–N(1)–C(6)	125.02(12)	C(19)–C(17)–C(20)	110.54(13)
C(5)–C(1)–C(2)	107.30(12)		

Although, all available proton donor groups (i.e. N–H from acetamido groups) participate into N–H···O intermolecular hydrogen bond formation in **5a** and **5b** (Table 2), linking molecules into endless chains. The hydrogen bonding pattern is different than in the structure of methyl 1′-acetamidoferrocene-1-carboxylate [21] in which dimerization via N–H···O bonds occur and further, dimers are interconnected into 3D network by the C–H···O hydrogen bonds. In the crystal structure of **5a** the chains are further joined by the C–H···O hydrogen bonds, while in **5b** there are no hydrogen bonds of the C–H···O type (Table 2).

Partial hydrolysis of amide-ester **5** by a double molar quantity of ethanolic-aqueous solution of sodium hydroxide gave 87% of 1′-(3-acetamidopropyl)ferrocene-1-carboxylic acid (**6**). The attempts to obtain the pure title compound **7** by refluxing of **5** with a large molar excess of the same reagent were unsuccessful. The reaction mixture was acidified to pH 5–7, but the desired amino acid did not precipitate. After evaporation to dryness, the obtained residue (contaminated with sodium chloride) could not be extracted by organic solvents (ether, chloroalkanes, alcohols). Extractions of aqueous solutions of the raw product (under either acidic or basic conditions) into diethyl ether or dichloromethane were unsuccessful too, indicating the presence of the ionic forms of 1′-(3-aminopropyl)ferrocene-1-carboxylic acid (**7**).

In order to overcome the encountered problems we have applied another strategy to obtain 1′-(3-aminopropyl)ferrocene-1-carboxylic acid (**7**) in the form of the stable *N*-Boc-derivative. By heating the crucial intermediate **4** in *tert*-butyl alcohol it was converted into carbamate **8** (92%) (Scheme 1).

The similar reaction sequence was made to obtain 1′-amino-1-ferrocenebutyric acid (**14**). 1′-Carboxy-1-ferrocenebutyric acid (**9**) (obtained by hydrolysis of ester-acid **3**) was partially esterified into acid-ester **10** which was converted into methyl 1′-azidocarbonyl-1-ferrocenebutyrate (**11**) in the same way as described for preparation of ester-azide **4**. Azide-ester **11** was rearranged and acylated by heating in acetic anhydride giving methyl 1′-acetamido-1-ferrocenebutyrate (**12**) in 67% yield. The attempt to obtain the pure amino acid **14** was unsuccessful. Similarly as described for conversion **5**→**7** here we faced the problems about isolation of reaction product too (Scheme 2).

One of the reasons for preparation of *N*-acetyl derivatives **5** and **12** is possibility to use them as model substances in the planned structural analysis of the derived peptides **IV**.

By heating the crucial intermediate **11** in *tert*-butyl alcohol it was converted into carbamate **15** followed by a little amount (according to TLC of reaction mixture) of symmetric urea derivative **16** (Scheme 3).

It is interesting to mention that the analogous products in a similar ratio were obtained in our previous work on 1′-aminoferrocene-1-carboxylic acid (**III** m, $n = 0$) [15]. Contrarily, in reaction of ester-azide **4** (with inserted trimethylene unit between carbazide function

Table 2
Hydrogen bond geometry (Å, °)

D–H···A	D–H	H···A	D···A	∠ D–H···A	Symmetry code
5a					
N1–H1N···O1	0.817(18)	2.012(18)	2.8201(12)	170.1(18)	$x, 3/2-y, -1/2+z$
C2–H2···O1	0.929(16)	2.572(16)	3.4825(13)	166.8(14)	$1-x, 1-y, 1-z$
5b					
N1–H1N···O4	0.76(2)	2.09(2)	2.838(2)	170(2)	$1-x, -1/2+y, 1/2-z$
N2–H2N···O1	0.811(19)	2.027(19)	2.823(2)	167(2)	$-x, 1/2+y, 1/2-z$
15					
N1–H1N···O3	0.79(2)	2.08(2)	2.8396(15)	162(2)	$x, -y, -1/2+z$
C7–H7···O3	0.93(2)	2.60(2)	3.2673(18)	129.2(16)	$x, -y, -1/2+z$
C18–H18A···O1	0.99(3)	2.57(3)	3.482(2)	153(2)	$3/2-x, -1/2+y, 1/2-z$

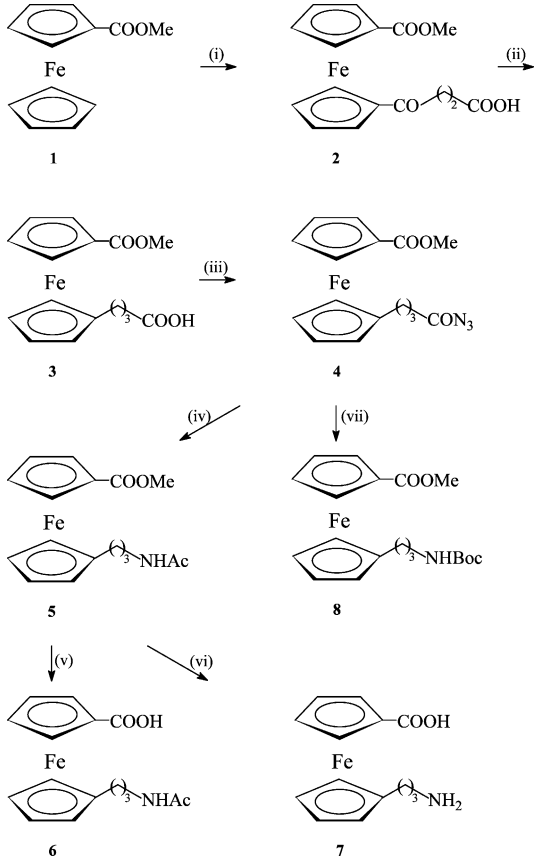
and ferrocene nucleus) with *tert*-butyl alcohol only the desired Boc-derivative **8** was isolated (Scheme 1).

One can assume that ester-azides in which ferrocene is directly connected with carbazide group gave *sym*-urea derivatives probably because of great electron-releasing ability of organometallic part facilitating pyrolytical cleavage and dimerization of carbamates or the corresponding intermediate isocyanates into these byproducts.

An X-ray single-crystal structure of **15** is shown in Fig. 6.

In the structure of **15** the main stereochemical features of ferrocene geometry is bond distances Fe1–Cg1 (C1–C5) 1.6496(7) and Fe1–Cg2 (C6–C10) 1.6568(7) Å as well as Cg1–Fe1–Cg2 angle being of 179.10(1)°. The Cp rings are twisted away slightly from the fully eclipsed conformation (the dihedral angle between planes calculated through atoms of two Cp rings is 1.54(9)°). The shortest and the longest Fe–C bond distances are Fe1–C2 2.044(2) and Fe1–C6 2.068(1) Å, respectively (Table 1). The intermolecular hydrogen bonds of the N–H···O type connect molecules along with C–H···O bonds into 3D network (Table 2).

The preliminary investigations showed that deprotection of Boc-derivatives **8** and **15** can be accomplished by introduction of gaseous HCl in solutions of these compounds in ethyl acetate. The obtained amino acid hydrochlorides are relatively unstable but they can be successfully used for synthesis of peptides **IV** by DCC/HOBt method. From the other side similar peptides can be prepared by condensation of methoxycarbonyl functions of **8** and **15**, as well as of acetamides **6** and **13** with natural amino acids. Almost certainly, the formation of intramoleculary-bonded β-sheets, as such observed in peptides derived from **III** (m, $n = 0$), is not likely in this case, due to a dominant contribution of "anti-periplanar" (i.e. 1,3′) conformation.

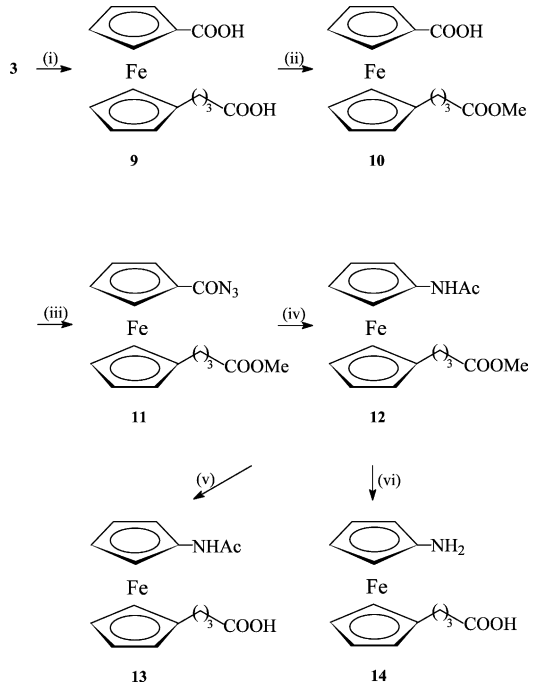


Scheme 1. (i) $(CH_2CO)_2O/AlCl_3$, CH_2Cl_2; (ii) Zn/Hg, HOAc, HCl; (iii) 1. NEt_3, ClCOOEt, acetone; 2. NaN_3, H_2O; (iv) Ac_2O; (v) 0.1 M NaOH/EtOH, H_2O (double molar quantity); (vi) 0.1 M NaOH/EtOH, H_2O (large molar excess); (vii) *t*-BuOH.

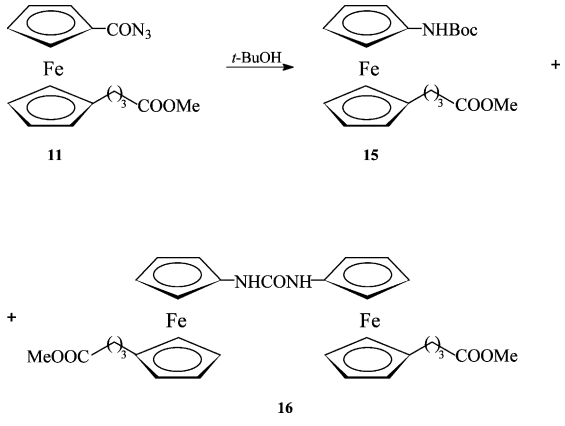
3. Experimental

3.1. General

Melting points were determined with a Buechi apparatus. The IR spectra were recorded for KBr pellets or



Scheme 2. (i) KOH, EtOH; (ii) MeOH, $BF_3 \cdot Et_2O$; (iii) 1. NEt_3, ClCOOEt, acetone; 2. NaN_3, H_2O; (iv) Ac_2O; (v) 0.1 M NaOH/EtOH, H_2O (double molar quantity); (vi) 0.1 M NaOH/EtOH, H_2O (large molar excess).



Scheme 3.

CH_2Cl_2 solutions with a Bomem MB 100 mid FTIR spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian EM 360 or Varian Gemini 300 spectrometer with Me_4Si as internal standard. Mass spectra (MS) were run on MAT 8200 (Finningan GmbH, Bremen). Products were purified by preparative thin layer chromatography on silica gel (Merck, Kieselgel 60 HF_{254}) using the mixtures CH_2Cl_2:EtOAc and CH_2Cl_2:MeOH and/or by recrystallization from (aqueous) EtOH.

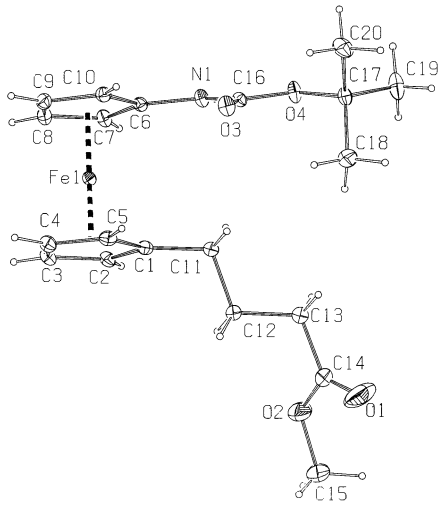


Fig. 6. An ORTEP view of the two independent molecules of **15** at 100 K showing atom numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

3.2. Methyl ferrocenecarboxylate (*1*)

Ferrocenecarboxylic acid (3.98 g, 17.3 mmol) was dissolved in MeOH (120 ml) and $BF_3 \cdot Et_2O$ (12 ml) was added. After refluxing for 4 h, 5% $NaHCO_3$ was added to pH ~ 8–9 and reaction mixture was extracted with CH_2Cl_2. Organic layer was washed with saturated solution of NaCl, dried with Na_2SO_4 and evaporated to dryness; orange crystals (3.28 g, 78%). m.p. 50–56 °C, m.p. [20] 68.5–70 °C. IR (CH_2Cl_2, cm^{-1}): 1711 w (ν C=O, $COOCH_3$). ^{1}H-NMR ($CDCl_3$, δ): 4.80 (t, 2H, H-2 H-5, Fc), 4.40 (t, 2H, H-3 H-4, Fc), 4.20 (s, 5 H, Fc unsubst. ring), 3.80 (s, 3H, $COOCH_3$). ^{13}C-NMR, APT ($CDCl_3$, δ): 171.1 ($COOCH_3$), 76.02 (C-1′, Fn), 71.01 (C-2, C-5, Fc), 69.8 (C-3, C-4, Fc), 69.2 (Fc unsubst. ring), 51.6 ($COOCH_3$).

3.3. 1′-Methoxycarbonyl-1-ferrocenesuccinic acid (*2*)

A solution of ester **1** (5.9 g, 24.3 mmol) and succinic anhydride (5.3 g, 52.9 mmol) in dry CH_2Cl_2 (40 ml) was added dropwise to a mixture of $AlCl_3$ (15.2 g, 114 mmol) and dry CH_2Cl_2 (40 ml). After stirring for 2 h at room temperature (r.t.), reaction mixture was poured on ice and extracted with CH_2Cl_2 to remove unreacted ester **1**. The aqueous layer was acidified with conc. HCl and dark orange crystals of **2** (6.2 g, 74%) were precipitated; m.p. 115.6–120.3 °C. IR (KBr, cm^{-1}): 1706 s (ν C=O, $COOCH_3$ and COOH), 1667 s (ν C=O, $CO(CH_2)_2COOH$). Anal. Calc. for $C_{16}H_{16}FeO_5$: C, 55.84; H, 4.69. Found: C, 56.02; H, 4.81%.

3.3.1. Methyl 1′-methoxycarbonyl-1-ferrocenesuccinate

$BF_3 \cdot Et_2O$ (0.16 ml) was added to a solution of **2** (50 mg, 0.15 mmol) in MeOH (1.5 ml). After stirring at r.t.

for 45 min, 5% aqueous solution of $NaHCO_3$ was added to pH ~ 8–9 and reaction mixture was extracted with CH_2Cl_2. Organic layer was washed with saturated solution of NaCl, dried with Na_2SO_4 and evaporated to dryness; orange crystals of Fn(COOMe)[CO(CH$_2$)$_2$COOMe], (45 mg, 91%). m.p. = 60–62 °C. IR (CH_2Cl_2, cm^{-1}): 1733 s (ν C=O, (CH$_2$)$_2$*CO*OCH$_3$), 1716 s (ν C=O, *CO*OCH$_3$), 1675 s (ν C=O, (*CO*(CH$_2$)$_2$COOCH$_3$). ^{1}H-NMR ($CDCl_3$, δ): 4.86 (s, 2H, H-2′, H-5′, Fn), 4.82 (s, 2H, H-2, H-5, Fn), 4.52 (s, 2H, H-3′, H-4′, Fn), 4.47 (s, 2H, H-3, H-4, Fn), 3.82 (s, 3H, COOCH$_3$), 3.73 (s, 3H, CH$_2$COOCH$_3$, Fn), 3.07 (t, 2H, α-CH$_2$), 2.77 (t, 2H, β-CH$_2$). ^{13}C-NMR, APT ($CDCl_3$, δ): 201.21 [*C*O(CH$_2$)$_2$], 173.36 [(CH$_2$)$_2$*C*OOCH$_3$], 170.74 (*C*OOCH$_3$), 79.45 (C-1, C-1′, Fn), 73.40 (C-2′, C-5′, Fn), 72.77 (C-2, C-5, Fn), 71.52 (C-3′, C-4′, Fn), 70.45 (C-3, C-4, Fn), 51.67 [(COO*C*H$_3$), (CH$_2$)$_2$COO*C*H$_3$], 34.23 (α-CH$_2$), 27.44 (β-CH$_2$).

3.4. 1′-Methoxycarbonyl-1-ferrocenebutyric acid (3)

To a solution of compound **2** (6.2 g, 17.9 mmol) in cold AcOH (82 ml) and conc. hydrochloric acid (123 ml) Zn-amalgam (30.1 g) was added in small portions during 45 min. Reaction mixture was stirred at r.t. for 1 h, then dissolved in water and extracted with CH_2Cl_2, washed with saturated solution of NaCl, dried with Na_2SO_4 and evaporated to dryness; orange oil (5.5 g, 94%). IR (CH_2Cl_2, cm^{-1}): 3100–2700 br (ν OH, COOH), 1746 m (ν C=O, COOCH$_3$), 1710 s (ν C=O, COOH).

3.5. Methyl 1′-(3-azidocarbonylpropyl)ferrocene-1-carboxylate (4)

Acid **3** (1.3 g, 3.9 mmol) was suspended in water (0.8 ml) and sufficient acetone was added to complete the solution. After cooling to 0 °C, Et_3N (0.64 ml, 4.6 mmol) in acetone (8.3 ml) was added. While maintaining the temperature at 0 °C a solution of ethyl chloroformate (0.48 ml, 5 mmol) in the same solvent (2.1 ml) was added and the mixture was stirred for 30 min at 0 °C. After that a solution of sodium azide (504.6 mg, 5.95 mmol) in water (1.4 ml) was added. The mixture was stirred for 1 h (0 °C), poured into excess of ice water, and extracted with CH_2Cl_2. The extracts were washed with 5% aqueous solution of $NaHCO_3$, saturated solution of NaCl, dried over Na_2SO_4 and evaporated in vacuo at r.t. to dryness to leave red oil of azide-ester **4** (1.38 g, 99%). IR (CH_2Cl_2, cm^{-1}: 2137 s (N_3), 1712 s (ν C=O, COOCH$_3$ and CON$_3$). ^{1}H-NMR ($CDCl_3$, δ): 4.73 (d, 2H, H-2, H-5, Fn), 4.36 (d, 2H, H-3, H-4, Fn), 4.10 (m, 4H, H-2′, H-3′, H-4′, H-5′, Fn), 3.80 (s, 3H, COOCH$_3$), 2.34 (m, 4H, α-CH$_2$, γ-*CH$_2$*), 1.80 (m, 2H, β-CH$_2$). ^{13}C-NMR, APT ($CDCl_3$, δ): 176.7 (*C*ON$_3$), 173.6 (*C*OOCH$_3$), 89.96 (C-1, Fn), 89.56 (C-1′, Fn), 71.64 (C-2, C-5, Fn), 70.5 (C-2′, C-5′, Fn), 69.59 (C-3, C-4, Fn), 70.45 (C-3′, C-4′, Fn), 51.67 [(COO*C*H$_3$), (CH$_2$)$_2$COO*C*H$_3$], 34.23 (α-CH$_2$), 30.23 (γ-CH$_2$), 27.44 (β-CH$_2$). Anal. Calc. for $C_{16}H_{17}FeN_3O_3$: C, 54.10; H, 4.82; N, 11.83. Found: C, 54.62; H, 4.57; N, 12.03%.

3.6. Methyl 1′-(3-acetamidopropyl)ferrocene-1-carboxylate (5)

A solution of azide-ester **4** (900 mg, 2.5 mmol) in Ac_2O (67 ml) was heated at 80 °C for 3 h. After cooling reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with 5% aqueous solution of $NaHCO_3$, saturated solution of NaCl, dried with Na_2SO_4 and evaporated to dryness giving a red oil; TLC-purification with CH_2Cl_2:EtOAc (5:1) gave red–orange crystals (545.4 mg, 63%). m.p. 68.2–72.3 °C. IR (CH_2Cl_2, cm^{-1}): 3446 m (ν N–H), 1709 s (ν C=O, COOCH$_3$), 1673 s (ν C=O, NHCOCH$_3$). ^{1}H-NMR ($CDCl_3$, δ): 5.88 (bs, 1H, NH), 4.73 (s, 2H, H-2, H-5, Fn), 4.36 (d, 2H, H-3, H-4, Fn), 4.10 (m, 4H, H-2′, H-3′, H-4′, H-5′, Fn), 3.80 (s, 3H, COOCH$_3$), 3.26 (m, 2H, α-CH$_2$), 2.28 (t, 2H, γ-CH$_2$), 1.98 (s, 3H, NHCOCH$_3$), 1.70 (m, 2H, β-CH$_2$). ^{13}C-NMR, APT ($CDCl_3$, δ): 171.96 (NH*C*OCH$_3$), 170.1 (*C*OOCH$_3$), 89.51 (C-1, Fn), 71.62 (C-2, C-5, Fn), 71.36 (C-1′, Fn), 70.51 (C-2′, C-5′, Fn), 69.39 (C-3, C-4, Fn), 68.81 (C-3′, C-4′, Fn), 51.40 [(COO*C*H$_3$), (CH$_2$)$_2$COO*C*H$_3$], 39.20 (α-CH$_2$), 30.10 (γ-CH$_2$), 25.53 (β-CH$_2$), 23.13 (NHCO*C*H$_3$). MS (FAB): $m/z = 343$ [M^+, 93%], 220 [M−CpCOOMe, 100%]. HRMS (CI) Calc. for $C_{17}H_{21}FeNO_3$: 343.08710. Found: 343.08700. Anal. Calc. for $C_{17}H_{21}FeNO_3$: C, 59.49; H, 6.17; N, 4.08. Found: C, 59.21; H, 5.98; N, 4.27%.

3.7. 1′-(3-Acetamidopropyl)ferrocene-1-carboxylic acid (6) and attempt to prepare 1′-(3-aminopropyl)ferrocene-1-carboxylic acid (7)

3.7.1. Procedure A

A solution of amide-ester **5** (300 mg, 0.87 mmol) in 0.1 M ethanolic solution of NaOH (17.1 ml) containing water (1 ml) was refluxed for 7 h. Thereupon reaction mixture (pH ~ 9) was acidified with 0.1 M HCl/EtOH to pH ~ 3–4 and evaporated to dryness to leave red–orange residue; it was dissolved in EtOH and chromatographed on TLC-plates with CH_2Cl_2:MeOH (9:1) giving orange crystals of **6** (250.6 mg, 87%). m.p. = 161–165 °C. IR (KBr, cm^{-1}): 3403 m (ν N–H), 3100–2900 b (ν OH, COOH), 1642 s (ν C=O, COOH and COCH$_3$). MS (FAB): $m/z = 329$ [M^+, 76%], 220 [M−CpCOOH, 100%]. HRMS (CI) Calc. for $C_{16}H_{19}FeNO_3$: 329.07144. Found: 329.07150. Anal. Calc. for $C_{16}H_{19}FeNO_3$: C, 58.38; H, 5.82; N, 4.26. Found: C, 57.92; H, 5.27; N, 3.97%.

3.7.2. Procedure B

In a similar way as described in Section 3.7.1, an ethanolic-aqueous solution of amide-ester **5** was refluxed with a large molar excess of NaOH for 4 h to obtain amino acid **7**. Reaction solution was acidified to pH ~ 6–7 and evaporated to dryness. The reaction product (contaminated with NaCl) could not be extracted by organic solvents (ethers, chloroalkanes, alcohols). Extractions of aqueous solutions of the row product (under either acidic or basic conditions) into Et_2O or CH_2Cl_2 were also unsuccessful.

3.8. *tert*-Butyl 1′-(methoxycarbonyl)-1-ferrocenepropylcarbamate (**8**)

A solution of azide-ester **4** (400 mg, 1.13 mmol) in dry *tert*-butyl alcohol (4.5 ml) was heated at 60 °C for 1.5 h. After stirring at r.t. for 16 h, reaction mixture was evaporated to dryness. Purification by column chromatography with CH_2Cl_2 and EtOAc (15:1) gave orange oil of carbamate **8** (360 mg, 92%). IR (CH_2Cl_2, cm^{-1}): 3449 m (*v* N–H), 1709 s (*v* C=O, $COOCH_3$ and $COOt$-Bu). ^{1}H-NMR ($CDCl_3$, δ): 5.91 (bs, 1H, NH), 4.72 (2H, H-2, H-5, Fn), 4.35 (d, 2H, H-3, H-4, Fn), 4.09 (m, 4H, H-2′, H-3′, H-4′, H-5′, Fn), 3.80 (s, 3H, $COOCH_3$), 3.13 (q, 2H, α-CH_2), 2.27 (t, 2H, γ-CH_2), 1.66 (m, 2H, β-CH_2), 1.44 [s, 9H, $COOC(CH_3)_3$]. ^{13}C-NMR, APT ($CDCl_3$, δ): 171.84 ($COOCH_3$), 155.88 [$COOC(CH_3)_3$], 89.71 [$C(CH_3)_3$], 78.92 (C-1, Fn), 71.70 (C-2, C-5, Fn), 71.41 (C-1′, Fn), 70.53 (C-2′, C-5′, Fn), 69.53 (C-3, C-4, Fn), 68.91 (C-3′, C-4′, Fn), 51.41 ($COOCH_3$), 40.18 (α-CH_2), 30.93 (γ-CH_2), 28.31 ($COOCH_3$), 25.55 (β-CH_2). MS (FAB): $m/z = 401$ [M^+, 84%], 345 (100%), 222 [M−CpNHCOO*t*Bu, 43%]. HRMS (CI) Calc. for $C_{20}H_{27}FeNO_4$: 401.12894. Found: 401.12890. Anal. Calc. for $C_{20}H_{27}FeNO_4$: C, 59.86; H, 6.78; N, 3.49%. Found: C, 60.21; H, 7.12; N, 3.02%.

3.9. 1′-Carboxy-1-ferrocenebutyric acid (**9**)

Ester-acid **3** (3 g, 9.1 mmol) was dissolved in EtOH and potassium hydroxide (11.5 g, 205 mmol) was added. After refluxing for 80 min, EtOH was removed in vacuo and the residuum was dissolved in 5% aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 to remove unreacted **3**. The aqueous layer was acidified with conc. HCl and orange crystals of compound **9** (2.5 g, 87%) were precipitated; m.p. 128–131 °C. IR (CH_2Cl_2, cm^{-1}): 3100–2800 bs (*v* OH, COOH), 1698 s (*v* C=O, COOH). Anal. Calc. for $C_{15}H_{16}FeO_4$: C, 56.99; H, 5.10. Found: C, 56.21; H, 4.87%.

3.10. Methyl-1′-carboxy-1-ferrocenebutyrate (**10**)

Acid **9** (2.5 g, 7.9 mmol) was dissolved in MeOH (75 ml) and $BF_3 \cdot Et_2O$ (7.5 ml) was added. After stirring at r.t. for 1 h, 5% aqueous solution of $NaHCO_3$ was added to pH ~ 8–9 and reaction mixture was extracted with CH_2Cl_2. Organic layer was washed with saturated solution of NaCl, dried with Na_2SO_4 and evaporated to dryness; orange crystals (2.4 g, 94%). m.p. = 68.6–74.4 °C. IR (CH_2Cl_2, cm^{-1}): 3100–2800 bs (*v* OH, COOH), 1731 s (*v* C=O, $COOCH_3$), 1675 s (*v* C=O, COOH). Anal. Calc. for $C_{16}H_{18}FeO_4$: C, 58.20; H, 5.50. Found: C, 57.83; H, 4.97%.

3.11. Methyl 1′-azidocarbonyl-1-ferrocenebutyrate (**11**)

Azide-ester **11** was prepared in a similar way as described for synthesis of azide-ester **4**; red oil (74%). IR (CH_2Cl_2, cm^{-1}: 2135 s (N_3), 1733 s (*v* C=O, $COOCH_3$), 1682 s (*v* C=O, CON_3). ^{1}H-NMR ($CDCl_3$, δ): 4.74 (d, 2H, H-2, H-5, Fn), 4.47 (d, 2H, H-3, H-4, Fn), 4.14 (d, 4H, H-2′, H-3′, H-4′, H-5′, Fn), 3.67 (s, 3H, $COOCH_3$), 2.32 (m, 4H, α-CH_2, γ-CH_2), 1.83 (m, 2H, β-CH_2). ^{13}C-NMR, APT ($CDCl_3$, δ): 180.16 (CON_3), 171.67 ($COOCH_3$), 88.95 (C-1, Fn), 88.56 (C-1′, Fn), 73.1 (C-2, C-5, Fn), 70.70 (C-2′, C-5′, Fn), 70.07 (C-3, C-4, Fn), 69.51 (C-3′, C-4′, Fn), 51.42 [$(CH_2)_3COOCH_3$], 33.35 (α-CH_2), 27.74 (γ-CH_2), 25.89 (β-CH_2). Anal. Calc. for $C_{16}H_{17}FeN_3O_3$: C, 54.10; H, 4.82; N, 11.83. Found: C, 54.78; H, 4.45; N, 12.14%.

3.12. Methyl 1′-acetamido-1-ferrocenebutyrate (**12**)

A solution of azide-ester **11** (1 g, 2.8 mmol) in acetic anhydride (76.4 ml) was heated at 80 °C for 6 h, as it was described for synthesis of compound **5**. After work up, dark yellow oil of amide-ester **12** (649.5 mg, 67%) was obtained. IR (CH_2Cl_2, cm^{-1}): 3436 m (*v* N−H), 1732 s (*v* C=O, $COOCH_3$), 1683 s (*v* C=O, $NHCOCH_3$). ^{1}H-NMR ($CDCl_3$, δ): 5.19 (bs, 1H, NH), 4.7 (s, 2H, H-2, H-5, Fn), 4.66 (s, 2H, H-3, H-4, Fn), 4.47 (d, 4H, H-2′, H-3′, H-4′, H-5′, Fn), 3.68 (s, 3H, $COOCH_3$), 2.36 (t, 2H, α-CH_2), 2.19 (t, 2H, γ-CH_2), 1.96 (s, 3H, $NHCOCH_3$), 1.76 (m, 2H, β-CH_2). ^{13}C-NMR, APT ($CDCl_3$, δ): 174.18 ($COOCH_3$), 167.29 ($NHCOCH_3$), 93.97 (C-1, Fn), 89.04 (C-1′, Fn), 71.36 (C-2, C-5, Fn), 70.87 (C-2′, C-5′, Fn), 69.35 (C-3, C-4, Fn), 67.16 (C-3′, C-4′, Fn), 51.44 [$(CH_2)_3COOCH_3$], 33.29 (α-CH_2), 27.04 (γ-CH_2), 25.46 (β-CH_2), 23.58 ($NHCOCH_3$). MS (FAB): $m/z = 343$ [M^+, 100%], 221 [M−CpNHCOCH$_3$, 31%)] (178, 43%). HRMS (CI) Calc. for $C_{17}H_{21}FeNO_3$: 343.08710. Found: 343.08700.

3.13. 1′-Acetamido-1-ferrocenebutyric acid (**13**) and attempt to prepare 1′-amino-1-ferrocenebutyric acid (**14**)

3.13.1. Procedure A

A solution of amide-ester **12** (300 mg, 0.87 mmol) in 0.1 M ethanolic solution of NaOH (17.1 ml) containing water (1.1 ml) was refluxed for 9 h, as it was described

for preparation of **6**. After work up, orange resin of **13** (178.9 mg, 62%) was obtained. IR (KBr, cm^{-1}): 3320 m (ν N–H), 3270–2860 bs (ν OH, COOH), 1690 s (ν C=O, COOH), 1656 s (ν C=O, $NHCOCH_3$). MS (FAB): $m/z = 329$ [M^+, 100%], 206 [M−CpNHCOCH$_3$, 16%], 178 [M−Cp$(CH_2)_3$COOH, 67%]. HRMS (CI) Calc. for $C_{16}H_{19}NO_3Fe$: 329.07144. Found: 329.07150. Anal. Calc. for $C_{16}H_{19}FeNO_3$: C, 58.38; H, 5.82; N, 4.26. Found: C, 57.89; H, 5.34; N, 3.97%.

3.13.2. Procedure B

In a similar way as described in Section 3.13.1, an ethanolic-aqueous solution of amide-ester **12** was refluxed with a large molar excess of NaOH for 4 h to obtain amino acid **14**. Reaction solution was acidified to pH ~ 6–7 and evaporated to dryness. The reaction product (contaminated with NaCl) could not be extracted by organic solvents (ethers, chloroalkanes, alcohols). Extractions of aqueous solutions of the row product (under either acidic or basic conditions) into Et_2O or CH_2Cl_2 were also unsuccessful.

3.14. tert-Butyl 1′-(3-methoxycarbonylpropyl)-1-ferrocenecarbamate (15) and dimethyl 1′,1′-ureylenedi(1-ferrocenebutyrate) (16)

A solution of azide-ester **11** (1 g, 2.89 mmol) in dry *tert*-butyl alcohol (25 ml) was heated at 70 °C for 12 h end evaporated to dryness. Purification by TLC with CH_2Cl_2 and EtOAc gave yellow resin of carbamate **15** (667 mg, 59%) followed by *sym*-urea derivative **16** (160 mg, 9%). m.p. 99–104 °C.

15: IR (CH_2Cl_2, cm^{-1}): 3436 m (νN–H), 1731 s [ν C=O, $(CH_2)_3COOCH_3$], 1715 s [ν C=O, $NHCOOC(CH_3)_3$]. ^{1}H-NMR ($CDCl_3$, δ): 5.79 (s, 1H, NH), 4.73 (s, 2H, H-2, H-5, Fn), 4.66 (s, 2H, H-3, H-4, Fn), 4.47 (d, 4H, H-2′, H-3′, H-4′, H-5′, Fn), 3.67 (s, 3H, CH_3COOCH_3, Fn), 2.33 (t, 4H, α-, γ-CH_2), 1.83 (m, 2H, β -CH_2), 1.49 [s, 9H, $NHCOOC(CH_3)_3$]. ^{13}C-NMR, APT ($CDCl_3$, δ): 173.9 [$(CH_2)_3COOCH_3$], 171.81 [$COOC(CH_3)_3$], 88.80 (C-1, Fn), 89.04 [$C(CH_3)_3$], 79.17 (C-1′, Fn), 69.53 (C-2, C-5, Fn), 68.87 (C-2′, C-5′, Fn), 65.25 (C-3, C-4, Fn), 60.20 (C-3′, C-4′, Fn), 51.35 [$(CH_2)_3COOCH_3$], 33.42 (α-CH_2), 28.18 [$(CH_3)_3$], 27.70 (γ-CH_2), 25.97 (β-CH_2). MS (FAB): $m/z = 401$ [M^+, 22%], 345 [M−C$(CH_3)_3$, 100%], 221 [M−CpNHCOO*t*BU, 42%]. HRMS (CI) Calc. for $C_{20}H_{27}FeNO_4$: 401.12894. Found: 401.12890. Anal. Calc. for $C_{20}H_{27}FeNO_4$: C, 59.86; H, 6.78; N, 3.49. Found: C, 60.13; H, 6.21; N, 3.87%.

16: IR (CH_2Cl_2, cm^{-1}): 3436 m (ν N–H), 1727 s [ν C=O, $(CH_2)_3COOCH_3$], 1713 s (C=O, NHCONH). ^{1}H-NMR ($CDCl_3$, δ): 6.62 (s, 1H, NH), 4.38 (s, 2H, H-2, H-5, Fn), 4.10 (s, 4H, H-2′ H-5′, H-3, H-4, Fn), 3.99 (s, 2H, H-3′, H-4′, Fn), 3.69 (s, 3H, CH_3COOCH_3, Fn), 2.36 (m, 4H, α-, γ-CH_2), 1.84 (m, 2H, β -CH_2). ^{13}C-NMR, APT ($CDCl_3$) δ/ppm: 174.18 [$(CH_2)_3COOCH_3$], 154.61 (NH*C*ONH), 95.13 (C-1, Fn), 88.73 (C-1′, Fn), 68.93 (C-2, C-5, Fn), 68.32 (C-2′, C-5′, Fn), 65.49 (C-3, C-4, Fn), 62.20 (C-3′, C-4′, Fn), 51.47 [$(CH_2)_3COOCH_3$], 33.36 (α-CH_2), 27.96 (γ-CH_2), 25.66 (β-CH_2). MS (FAB): $m/z = 628$ [M^+, 5%], 463 [M−Cp$(CH_2)_3$COOMe, 1%], 327 (94%), 301 (100%). HRMS (CI) Calc. for $C_{31}H_{36}Fe_2N_2O_5$: 628.13232. Found: 628.13220. Anal. Calc. for $C_{31}H_{36}Fe_2N_2O_5$: C, 59.26; H, 5.78; N, 4.46. Found: C, 59.56; H, 5.52; N, 4.32%.

3.15. X-ray single crystal analysis of compounds 5 and 15

Crystal data and details of the structure determination for **5a**, **5b** and **15** are summarized in Table 3. Single crystals suitable for X-ray single crystal diffractometry were obtained from toluene/CH_2Cl_2 (1:2) solution by liquid diffusion for **5a** and **5b** and by evaporation from ethanol for **15**. In the toluene/CH_2Cl_2 solution of **5** two different kinds of single crystals appeared (**5a** and **5b**).

The data collections were carried out at 100 K for **5a** and for **15** and at 297 K for **5b** on Bruker automatic diffractometer with CCD area detector.

Data collection was controlled by the Bruker SMART program [22]. The data were corrected for the Lorenz-polarization effects by the Bruker SAINT program [23]. The multi-scan absorption correction was performed by the SADABS program [24]. The structures were solved by direct methods implemented in the SHELXS program [25].

The applied refinement procedure based on the F^2 values [23] against all reflections included anisotropic model for all non-H atoms by using the SHELXL program [26].

In all three structures the hydrogen atoms were found in the Fourier electron-density maps and refined freely (C–H 0.925(15)–0.999(17) Å and N–H 0.819(19) Å in **5a**; C–H 0.86(4)–1.00(3) and N1–H1N 0.76(2) and N2–H2N 0.81(2) Å in **5b**; N1–H1N 0.78(2) and C–H 0.905(19)–1.04(3) Å in **15**).

Graphical work has been performed by the program PLATON98 and Bruker SHELXTL [27,28].

4. Conclusion

The rational and convenient syntheses of *N*-acetyl and *N*-Boc derivatives of heteroannularly substituted ferrocene amino acids-1′-(3-aminopropyl)ferrocene-1-carboxylic acid (**7**) and 1′-amino-1-ferrocenebutyric acid (**14**), as well as of the corresponding methyl esters were accomplished. Having in mind the successful preparation of the analogous derivatives of 1′-amino-ferrocene-1-carboxylic acid [15] one can conclude that the syntheses described could be applied as a general method for preparation of amino acids of the type **III**

Table 3
Crystal data and details of the structure determination for **5a**, **5b** and **15**

Compound	**5a**	**5b**	**15**
Formula	$C_{17}H_{21}FeNO_3$	$C_{17}H_{21}FeNO_3$	$C_{20}H_{27}FeNO_4$
M_r	343.20	343.20	401.28
Color and habit	Red–orange, prism	Red–orange, irregular	Yellow, prism
Crystal system, space group	Monoclinic, $P2_1/c$ (No. 14)	Monoclinic, $P2_1/c$ (No. 14)	Monoclinic, $C2/c$ (No. 15)
Crystal dimensions (mm^3)	$0.40 \times 0.28 \times 0.26$	$0.22 \times 0.20 \times 0.15$	$0.21 \times 0.20 \times 0.14$
Temperature (K)	103(2)	297(2)	103(2)
Unit cell parameters			
a (Å)	10.7292(6)	9.2232(5)	39.207(2)
b (Å)	17.1165(10)	17.5903(10)	10.1411(5)
c (Å)	9.1026(5)	19.9254(11)	9.7663(5)
β (°)	111.0980(10)	95.3980(10)	93.877(2)
V ($Å^3$)	1559.60(15)	3218.3(3)	3874.2(3)
Radiation, Mo–K_α (Å)	0.71073	0.71073	0.71073
Z	4	8	8
Density (calculated)	1.462	1.417	1.376
μ (mm^{-1})	0.979	0.948	0.803
θ Range for data collection (°)	2.03 to 32.00	1.55 to 29.13	2.07 to 32.02
h, k, l range	$-15 \le h \le 14$, $0 \le k \le 25$, $0 \le l \le 13$	$-12 \le h \le 12$, $0 \le k \le 24$, $0 \le l \le 27$	$-58 \le h \le 58$, $0 \le k \le 15$, $0 \le l \le 14$
Diffractometer	CCD area detector		
Scan type	ω	ω	ω
Number of measured reflections	28 473	36 159	33 578
Number of independent reflections (R_{int})	5238 (0.0209)	8662 $R_{int} = 0.0408$	6655 (0.0378)
Number of observed reflections, $I \ge 2\sigma(I)$	4717	6482	5642
Number of refined parameters	283	565	343
R, wR [$I \ge 2\sigma(I)$]	0.0262; 0.0667	0.0340; 0.0803	0.0371; 0.0925
R, wR [all data]	0.0309; 0.0698	0.0551; 0.0919	0.0478; 0.0987
g_1, g_2 in w	0.0376; 0.5363	0.0432; 0.9460	0.0454; 4.9176
Goodness-of-fit on F^2, S	1.062	1.006	1.126
Max., min. electron density (e $Å^{-3}$)	0.546; −0.220	0.351 and −0.279	1.254; −0.458
Maximum Δ/σ	0.001	0.001	0.004
Absorption correction type	Semi-empirical from equivalents		
Range of transmission factors min., max.	1.0000 and 0.8348	1.0000 and 0.7807	1.0000 and 0.8425

(m, $n = 0$, 1, 2, 3...). Moreover, by coupling of these compounds with natural amino acids and/or dipeptides the corresponding oligopeptides containing *N*- and *C*-ferrocenyl, as well as *nonterminal* ferrocene amino acids can be prepared in good yields [18].

5. Supplementary material

Atomic coordinates and equivalent isotropic displacement parameters, calculated hydrogen atom parameters, anisotropic thermal parameters and bond lengths and angles have been deposited and allocated the deposition numbers at the Cambridge Crystallographic Data Centre, CCDC Nos. 210594 for **5a**, 210595 for **5b** and 210596 for **15**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). All structural factors tables are available from authors upon request.

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