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XXXIV *. BRIDGE ENLARGEMENT REACTION OF MULTIBRIDGED FERROCENOPHANES WITH DIAZOMETHANE AND SYNTHESES OF SOME FERROCENOPHANES WITH TETRAMETHYLENE BRIDGES BY APPLICATION OF THE REACTION

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Summary

Bridge enlargement reactions of α-oxo[3]ferrocenophane derivatives with diazomethane in the presence of methanol or $BF_3 \cdot OEt_2$ have been studied. Some new multibridged ferrocenophanes with tetramethylene bridges have been synthesized by application of the enlargement reaction.

Previously, we have synthesized several di-, tri- and tetra-bridged ferrocenophanes [1—4] with tetramethylene chains with the ultimate purpose of synthesizing pentabridged ferrocenophanes **. It is known [6] that the one-step formation of a tetramethylene bridge by cyclization of butyric acid derivatives is impossible due to selective occurrence of homoannular cyclization. Thus, formation of the tetramethylene bridges in the above ferrocenophanes were achieved by enlargement of α-oxo-trimethylene bridges, which are formed by heteroannular cyclization of a propionic acid side chain with diazomethane.

The reaction with diazomethane would be one of the key-steps in the synthesis of superferrocenophane with five tetramethylene bridges. However, sterically hindered α-oxo-trimethylene bridges adjacent to another bridge not be enlarged by the reaction using methanol as a catalyst, while bridge enlargement of α-oxo[3]ferrocenophanes without an adjacent bridge proceeds readily under the same conditions [3]. Further examination resulted in enlargement of the α-oxo-bridge adjacent to the other bridge by treatment with diazomethane in the presence of $BF_3 \cdot OEt_2$ in benzene as a solvent ***. Further-

* For part XXXIII, see ref. 1.

** The compound may be described as a "superferrocenophane" since its cage structure is analogous to that of Boekelheide's "superphane" [5].

*** Application of this reaction resulted in successful syntheses of [4][4][4]- and [4][4][4][4]-ferrocenophanes previously reported [4,7].

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more, it was found that the ratios of the resulting α- and β-ketones were dependent on the catalyst and existence of the adjacent bridge. One of the authors has already suggested that predominant production of α-ketone in the reaction with $BF_3 \cdot OEt_2$ in comparison with methanol was due to its higher strength as Lewis acid [8]. In the present paper we report on the further experimental results and discuss the bridge enlargement reaction.

Some ferrocenophanes have been prepared in order to serve as substrates for the examination of the bridge enlargement, and new multibridged ferrocenophanes with tetramethylene bridges have been synthesized by application of the reaction to ferrocenophanes with α-oxo-methylene bridges sterically hindered by other tetramethylene ones. These syntheses are also described in this paper.

Results and discussion

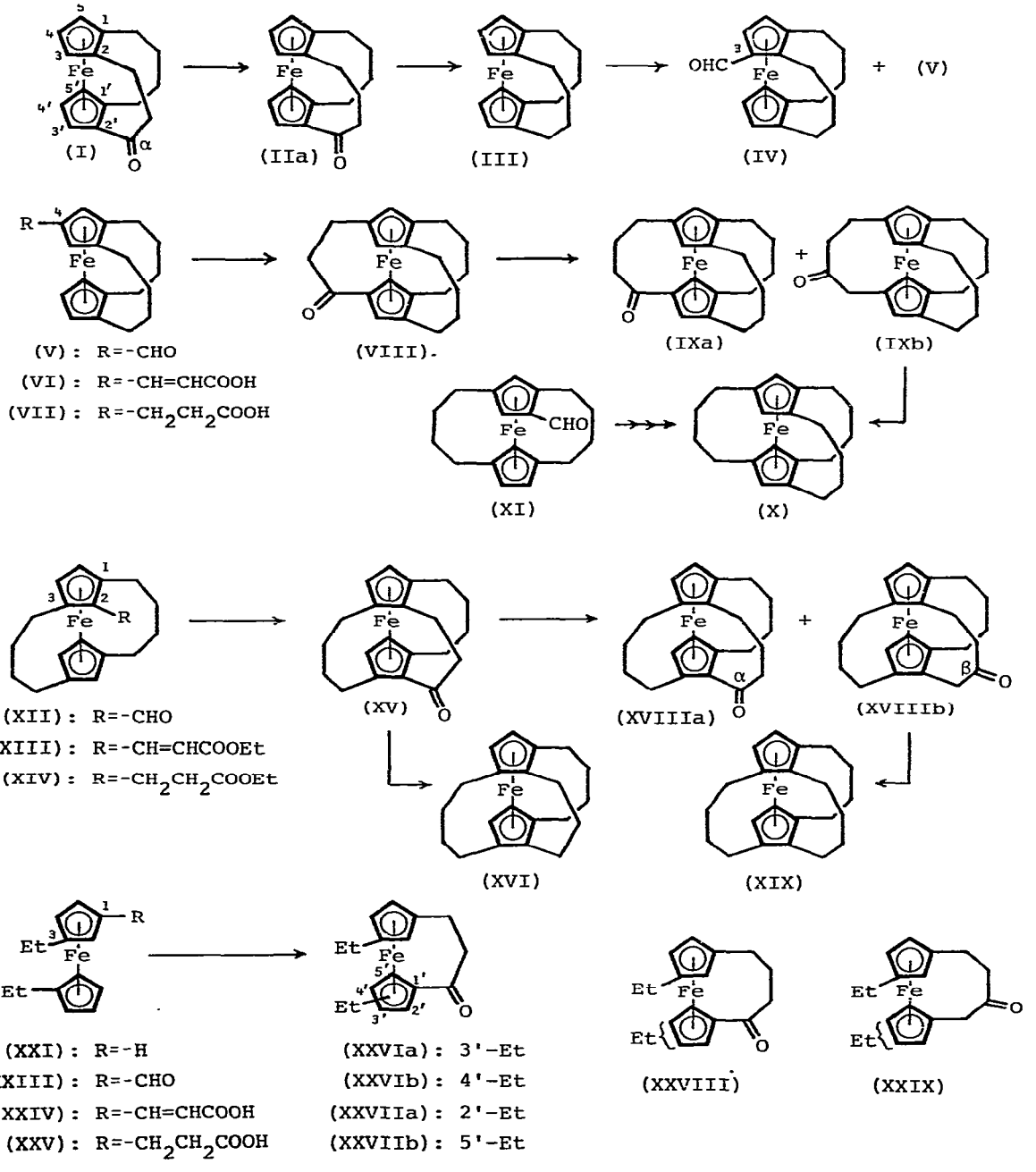
Syntheses of multibridged ferrocenophanes *

Bridge enlargement of [4](1,1′)-α-oxo[3](2,2′)ferrocenophane (I) with diazomethane in ether and methanol was unsuccessful [3], but use of $BF_3 \cdot OEt_2$ in benzene instead of methanol as a catalyst gave α-oxo[4][4]ferrocenophane (IIa). The ^1H and ^{13}C NMR spectra of the reduction product III of IIa indicated its symmetric structure; proton and carbon signals of cyclopentadienyl (Cp) rings appeared as only one singlet at δ 3.97 ppm and three peaks at δ 66.807, 68.320 and 85.812 ppm, respectively. Treatment of III with dimethylformamide(DMF)/$POCl_3$ gave two formylated products (IV and V). 4-Formyl[4][4]-ferrocenophane (V), which showed a singlet signal of formylated Cp ring protons at δ 4.59 ppm in the ^1H NMR, was converted into [4][4]-α-oxo[3]ferrocenophane (VIII) by condensation with malonic acid, catalytic hydrogenation and then cyclization with trifluoroacetic anhydride (TFAA). In the ^1H NMR spectrum of VIII the signals of the Cp ring protons appeared as only two singlets at δ 4.48 and 4.68 ppm. Bridge enlargement of VIII was performed with diazomethane in the presence of methanol to afford two isomeric ketones (IXa and IXb). One of them (IXb) was a β-ketone because of appearance of an isolated methylene proton signal as a singlet at δ3.21 ppm in the ^1H NMR, and the other (IXa) which showed a ν(C=O) band of the conjugated carbonyl group at 1640 cm^{-1} in the IR spectrum was an α-ketone. The reduction product (X) of IXb exactly agreed with [4](1,1′)[4](2,2′)[4](4,4′)ferrocenophane, which was prepared from formylferrocenophane XI via five steps [4]. Thus, the structure of ferrocenophanes II—X were confirmed.

Tribridged ferrocenophanes with three bridges adjacent to each other were synthesized, since the reactions employed in the synthesis could be regarded as model reactions for the synthesis of tetra- and penta-bridged ferrocenophanes. Condensation of 2-formyl[4][4]ferrocenophane (XII), which was the minor product in the formylation of [4](1,1′)[4](3,3′)ferrocenophane [3], was not accomplished by the usual method using malonic acid/piperidine but by the Reformatsky reaction with ethyl bromoacetate/Zn to give the acrylate deriva-

* The nomenclature and numbering system of the ferrocenophanes are according to those of previous papers [2,3]. Most compounds described in this paper were obtained as racemic mixtures, although only one of each enantiomorphs is shown in Scheme 1.

SCHEME 1
SYNTHESES OF FERROCENOPHANES *



tive (XIII). Cyclization of the hydrolysis product of XIV with polyphosphate ester (PPE) in dichloromethane gave [4][4]-α-oxo[3]ferrocenophane (XV) in good yield, while treatment of XIV with TFAA did not give a tribridged product but only the recovered starting material. The tribridged structure of XV was

supported by ^{1}H NMR spectroscopy; Cp ring proton signals appeared as only two singlets (each 2 H) at δ 3.86 and 4.12 ppm. The reduction product XVI of XV with $LiAlH_4/AlCl_3$ showed only one singlet signal of Cp ring protons in its ^{1}H NMR spectrum. The symmetric tribridged structure was determined by means of X-ray crystallographic analysis *. On the other hand, bridge enlargement of the ketone XV with diazomethane in the presence of $BF_3 \cdot OEt_2$ gave two isomeric ketones (XVIIIa and XVIIIb). The singlet signal of the isolated methylene protons at δ 3.29 ppm and the conjugated carbonyl band at 1655 cm^{-1} were observed in the ^{1}H NMR of the β-ketone XVIIIb and the IR of the α-ketone XVIIIa, respectively. The β-ketone XVIIIb was reduced with $LiAlH_4/AlCl_3$ to give [4][4][4]ferrocenophane XIX, of which the ^{1}H and ^{13}C NMR spectra showed only one singlet signal of Cp ring protons and three peaks of Cp ring carbons, respectively, as expected from its structure. Reduction of both XV and XVIIIb with $LiAlH_4/AlCl_3$ gave the corresponding alcohols in considerable yields (ca. 40%). The formation of incomplete reduction products indicate that the carbonyl groups are sterically hindered by two adjacent bridges [3].

The results of the above reactions suggest the possibility to synthesize tetra- and penta-bridged ferrocenophanes. In fact, tetrabridged [4][4][4][4]ferrocenophane could be synthesized by the above reaction route [7].

Diethyl[3]ferrocenophane was prepared in order to be used as a substrate in the examination of alkyl effects on bridge enlargement reactions. Formylation of 1,1'-diethylferrocene (XXI) gave two regio isomeric compounds (XXII and XXIII) in a ratio of ca. 1/3. The major product (XXIII, 47%), of which the signal of two protons adjacent to formyl group appeared at δ4.61 ppm, was the 3-formyl isomer. The cyclization products given by treatment of propionic acid (XXV) with TFAA were separated into two components (XXVI and XXVII) by column chromatography. The appearance of two double doublets (1/1 intensity ratio, J = 1.5 and 2.6 Hz), which did not change each other by spin-decoupling, at low field (δ 4.78 and 4.92 ppm) in the ^{1}H NMR spectrum of XXVII indicated that the component was a mixture (1/1) of two isomeric ferrocenophanes (XXVII and XXVIIb) possessing *ortho*-substituted Cp rings. The ^{1}H NMR spectrum of the other component (XXVI) indicated this was a mixture (ca. 1/3) of two *meta*-substituted ferrocenophanes (XXVIa and XXVIb); the bridge methylene protons appeared as only one singlet due to the absence of steric hindrance. The ratio of the mixture was determined by comparison of intensities of methyl and Cp ring proton signals. Both mixtures could not be separated into each isomer by any further chromatography over column or thin layered silica gel. The mixture of XXVI was provided as a substrate without isolation, because the alkyl effect of the two isomers XXVIa and XXVIb on the reactivity of the carbonyl group in bridge enlargement should be almost similar to each other.

Bridge enlargement reaction of α-oxo[3]ferrocenophanes with diazomethane

The reaction of ketones with diazomethane has been applied to ring expansion and elongation of carbon chain [2—4,7—12]. House et al. [9] suggested that addition of protic agents or Lewis acids in the reaction was required to

* The X-ray crystallographic results will be published elsewhere.

TABLE 1

BRIDGE ENLARGEMENT REACTIONS OF KETONES WITH DIAZOMETHANE IN THE PRESENCE OF METHANOL OR $BF_3 \cdot OEt_2$

Entry No.	Compound	Methanol			$BF_3 \cdot OEt_2$		
		α-Ketone (%)	β-Ketone (%)	α/β	α-Ketone (%)	β-Ketone (%)	α/β
1	XXX	3.2	79	0.041	40 [a]	15	2.7
2	XXX	—	—	—	38 [a]	29	1.3 [b]
3	XXVI	7.6	78	0.097	13	26	0.50
4	XXXI	3.7	91	0.041	17	28	0.61
5	XXXVI	—	—	—	75	15	5.0 [b]
6	VIII	2.7	77	0.035	5.8	3.8	1.5
7	I	—	—	—	59	trace	large
8	XXXII	—	—	—	63 [a]	10	6.3
9	XXXIII	—	—	—	20	9.8	2.0
10	XXXVII	—	—	—	49	trace	large [b]
11	XV	—	—	—	11	45	0.24
12	XXXV	—	—	—	27	37	0.73
13	XXXVIII	2.4	39	0.062 [c]	8.0	28	0.28 [c]
14	XXXIX	21	13	1.6 [c]	29	7.9	3.7 [c]

[a] The yields include those of α-oxo[5]ferrocenophanes which were formed by further bridge enlargement of α-oxo[4]ferrocenophanes. [b] The data are those already described by one of the authors [8]. [c] Data reported by House et al. [9].

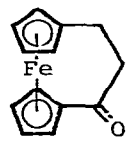
prevent generation of epoxide and thus the formation of the ring expansion product in good yield by migration of the alkyl chain. Furthermore, they indicated that formation of β-ketone in the treatment of acetophenone with diazomethane occurred in preference to that of α-ketone due to predominant migratory aptitude of phenyl groups to that of alkyl groups. In the bridge enlargement of α-oxo[3]ferrocenophanes too, β-ketones were predominantly formed when methanol was used as a catalyst [2,3,8,10]. However, it was also found that use of $BF_3 \cdot OEt_2$ as a catalyst in benzene as a solvent unexpectedly increased production of α-ketones [4,8]. Thus, an investigation of bridge enlargement using α-oxo[3]ferrocenophanes, prepared in this study and already reported, was carried out. The results are shown in Table 1 together with the data already described, and can be summerized as followed:

(1) When methanol was used as a catalyst, formation of β-ketones was overwhelmingly predominant, and the reaction of α-oxo-methylene bridges adjacent to other bridges could afford no enlargement product but only the recovered starting material.

(2) In the reaction with $BF_3 \cdot OEt_2$ in benzene, bridge enlargement occurred even if the α-oxo-methylene bridge was sterically hindered by adjacent bridges. Formation of α-ketone generally increased in comparison with the use of methanol.

(3) Substitution of Cp rings with alkyl group at the *meta* position decreased formation of the α-ketone compared with that for XXX (Entries 1—3).

(4) The presence of one bridge at the position adjacent to the ketone greatly increases formation of the α-ketone in the reaction with $BF_3 \cdot OEt_2$ (Entries 7, 8, 10).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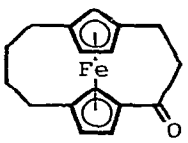
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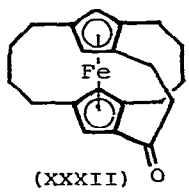
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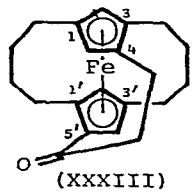
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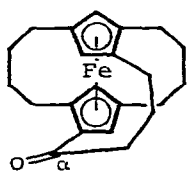
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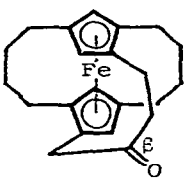
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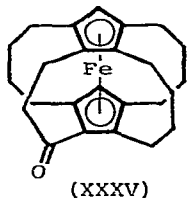
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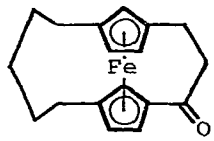
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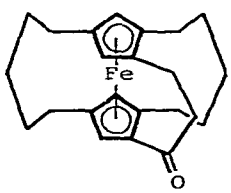
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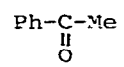
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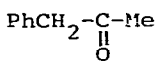
(XXXIX)

(5) Ratios of α/β in the compounds possessing ketones surrounded by two bridges are rather smaller than in XXX (Entries 11, 12).

House et al. [9] described that the decrease of yield of β-ketone in the reaction with $BF_3 \cdot OEt_2$ (Entries 13, 14) could possibly be attributed to complexing of the BF_3 with the aromatic ring. However, it seems reasonable that BF_3 is predominantly coordinated by the lone pair of the carbonyl group rather than by the π-electrons of the aromatic ring, because lack of complexing of BF_3 with the carbonyl group should cause formation of an epoxide but not bridge enlargement by migration [9,12], and because additional complexing of BF_3 at the aromatic ring would decrease the reactivity of ketone. We consider that the favorable production of α-ketones when using $BF_3 \cdot OEt_2$ reflects the stability of the intermediate or transition state in the migration, as recently described by one of the authors [8].

Increase in yields of α-ketones in the reaction of the compounds possessing a bridge adjacent to the ketone suggests a steric effect in the migration. The steric

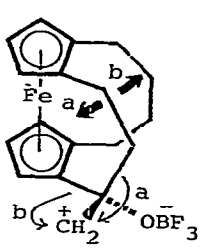

Fig. 1. An intermediate or a transition state, which is assumed to be found by attack of diazomethane from the opposite direction of the tetramethylene bridge, in the bridge enlargement reaction of α-oxo[3]-ferrocenophanes with an adjacent bridge.

effect from a bridge adjacent to the α-oxo-methylene would prevent migration of the Cp ring but accelerate that of the methylene chain in the intermediate or transition state, as shown in Fig. 1. The behavior of compound XXXIII (Entry 9) can be explained by considering that the steric hindrance of the bridge adjacent to the slant bridge is considerably smaller than that adjacent to the usual bridge. On the other hand, the ratios of α/β in XV and XXXV (Entries 11,12) are almost similar to those of the compounds without adjacent bridges (Entries 3, 4). The lack of steric effect in XV and XXXV arises, possibly, from there being no predominance in the direction of migration, since their oxomethylene chains are surrounded on both sides by the two equivalent tetramethylene bridges.

Experimental

All melting points are uncorrected. IR spectra were measured using Hitachi-Perkin-Elmer model 225 and Hitachi model 215 infrared spectrometers. All IR data are given in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained with a JEOL JNM FX-100 spectrometer at 100 and 25.1 MHz, respectively, at room temperature using tetramethylsilane as an internal standard. All chemical shifts and coupling constants of the NMR spectral data are shown as δ values in ppm and Hz, respectively. Mass spectra were obtained from Hitachi model RMU-7M and M-80 double focusing spectrometers using the direct insertion method at 70 eV ionizing energy. Fragment ion peaks and their intensities in parentheses are given in *m/z* and relative intensities vs. the base peak, respectively. High resolution mass spectra were analyzed on Hitachi model 002 and M-003 data processing systems.

The substrates used for the bridge enlargement reaction were prepared according to the procedures already reported by us [2—4], except for the ferrocenophanes described in this paper. The bridge enlargement products were identified by comparison with the authentic samples already reported.

General procedures

Formylation of ferrocenophanes with $DMF/POCl_3$ in chloroform, condensation of formylferrocenophanes with malonic acid/piperidine in pyridine, catalytic hydrogenation of acrylic acid derivatives with Pd-C in ethanol, cyclization of propionic acid derivatives with trifluoroacetic anhydride (TFAA) in dichloromethane, and reduction of ketones with $LiAlH_4/AlCl_3$ in ether were carried out according to the procedures described in the previous papers [2,3].

Treatment of α-oxo[3]ferrocenophane derivatives with diazomethane

(a) A solution of diazomethane in ether in excess was added to a solution of α-oxo[3]ferrocenophane derivative in ether/methanol. After stirring for the required time, the mixture was evaporated under a reduced pressure. The residue was column-chromatographed over silica gel and separated into bridge-enlarged isomeric α- and β-ketones, the starting material and other products.

(b) To a stirred solution of α-oxo[3]ferrocenophane derivative in dry benzene was slowly added a solution of $BF_3 \cdot OEt_2$ (1.5 mol eq. to substrate) in dry benzene. An ether solution of diazomethane, free from alcohol and dried over

KOH pellets, was added at once to the above complex solution with vigorously stirring. The reaction mixture was stirred for 5 min, and poured into water. The separated organic solution was washed with saturated aq. NaCl, dried over Na_2SO_4 and evaporated. The residue was column-chromatographed over silica gel.

[4](1,1')[4](2,2')Ferrocenophane (III)

Bridge enlargement of [4](1,1')-α-oxo[3](2,2')ferrocenophane (I) [3] (0.51 g, 1.7 mmol) in dry benzene (20 ml) with diazomethane in ether (100 ml) and $BF_3 \cdot OEt_2$ (0.40 ml, 3.3 mmol) gave 0.31 g (60%) of [4](1,1')-α-oxo[4](2,2')-ferrocenophane (IIa) and traces of the corresponding isomeric β-ketone (IIb). The α-ketone IIa was recrystallized from hexane to give orange-yellow prisms, m.p. 89—90°C. (Found: M^+, 308.0866. $C_{18}H_{20}OFe$ calcd.: mol. wt., 308.0862). IR spectrum (KBr): 1650 [ν(C=O)]. ^1H NMR spectrum ($CDCl_3$): 1.40—3.20 (14 H, m, $-CH_2-$), 3.90—4.30 (3 H, m, 3,4,5-H), 4.37 and 4.51 (2 H and 1 H, an ABX system, 3',4',5'-H). Mass spectrum: 308 (M^+, 100), 280 ($[M - CO]^+$, 12), 265 ($[M - COCH_3]^+$, 10).

Reduction of IIa (0.31 g, 1.0 mmol) with $LiAlH_4$ (0.11 g, 3.0 mmol)/$AlCl_3$ (0.27 g, 2.0 mmol) in ether (20 ml) gave [4](1,1')[4](2,2')ferrocenophane (III) (0.21 g, 71%), which was recrystallized from hexane to give yellow needles, m.p. 120—122°C. (Found: C, 73.65; H, 7.60; M^+, 294.1066. $C_{18}H_{22}Fe$ calcd.: C, 73.48; H, 7.54%, mol. wt., 294.1069.) ^1H NMR spectrum ($CDCl_3$): 1.93 and 2.35 (each 8 H, m, $-CH_2-$), 3.97 (6 H, s, Cp H). ^{13}C NMR spectrum ($CDCl_3$): 24.267 and 25.291 (methylene C), 66.807 (4,4'-C), 68.320 (3,3',5,5'-C), 85.812 (1,1',2,2'-C). Mass spectrum: 294 (M^+, 100), 266 ($[M - C_2H_4]^+$, 14).

[4](1,1')[4](2,2')-α-oxo[3](4,4')Ferrocenophane (VIII)

Formylation of [4][4]ferrocenophane (III) (0.29 g, 1.0 mmol) with DMF (0.38 ml, 5.0 mmol) and $POCl_3$ (0.46 ml, 5.0 mmol) in chloroform (20 ml) gave 3- and 4-formyl[4](1,1')[4](2,2')ferrocenophane (IV: 59 mg, 18%; V: 0.23 g, 72%). Recrystallization of 3-formylferrocenophane (IV) from hexane afforded brownish red granules, m.p. 95—98°C. (Found: M^+, 322.1006. $C_{19}H_{22}OFe$ calcd.: mol. wt., 322.1018.) IR spectrum (KBr): 1670 [ν(C=O)]. ^1H NMR spectrum ($CDCl_3$): 1.75—3.00 (16 H, m, $-CH_2-$), 3.90 and 4.13 (1 H and 2 H, an ABX system, 3',4',5'-H), 4.45 (1 H, d, J = 2.6, 5-H), 4.57 (1 H, d, J = 2.6, 4-H), 10.12 (1 H, s, —CHO). Mass spectrum: 322 (M^+, 100), 293 ($[M - CHO]^+$, 18).

4-Formylferrocenophane (V) was recrystallized from hexane to give brownish red needles, m.p. 75—78°C. (Found: C, 71.59; H, 7.04; M^+, 322.1037. $C_{19}H_{22}$-OFe calcd.: C, 70.82; H, 6.88%; mol. wt., 322.1018.) IR spectrum (KBr): 1675 [ν(C=O)]. ^1H NMR spectrum ($CDCl_3$): 1.80—2.55 (16 H, m, $-CH_2-$), 4.16 (3 H, an A_2B system, 3',4',5'-H), 4.59 (2 H, s, 3,5-H), 9.76 (1 H, s, —CHO). Mass spectrum: 322 (M^+, 100), 293 ($[M - CHO]^+$, 9).

Condensation of 4-formyl[4][4]ferrocenophane (V) (0.28 g, 0.85 mmol) with malonic acid (0.18 g, 1.7 mmol) and piperidine (0.15 g, 1.7 mmol) in pyridine (30 ml) gave 4-(2-carboxyvinyl)[4](1,1')[4](2,2')ferrocenophane (VI) (0.27 g, 85%), which was recrystallized from hexane to give dark red granules, m.p. 203—205°C. (Found: M^+, 364.1096. $C_{21}H_{24}O_2Fe$ calcd.: mol. wt., 364.1123.) IR spectrum (KBr): 1680 and 1615 [ν(C=O)] and ν(C=C)]. ^1H

NMR spectrum ($CDCl_3$): 1.60—2.50 (16 H, m, $-CH_2-$), 3.79 and 4.16 (1 H and 2 H, an A_2X system, 3′,4′,5′-H), 4.35 (2 H, s, 3,5-H), 5.89 and 7.59 (each 1 H, an AX system, J = 16, =CH—). Mass spectrum: 364 (M^+, 100), 320 ([M — CO_2]$^+$, 12).

Catalytic hydrogenation of acrylic acid (VI) (55 mg, 0.15 mmol) with Pd-C (10 mg) in ethanol (50 ml) gave 4-(2-carboxyethyl)[4](1,1′)[4](2,2′)ferrocenophane (VII) (55 mg, quant.), which was recrystallized from hexane to give yellow needles, m.p. 128—132°C. (Found: M^+, 366.1262. $C_{21}H_{26}O_2Fe$ calcd.: mol. wt., 366.1280.) IR spectrum (KBr): 1700 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.60—2.50 (16 H, m, —CH_2— of bridges), 2.60 (4 H, s, —CH_2— of propionic acid moiety), 3.74 and 4.06 (1 H and 2 H, an A_2X system, 3′,4′,5′-H), 3.96 (2 H, s, 3,5-H). Mass spectrum: 366 (M^+, 100), 307 ([M — CH_2COOH]$^+$, 14).

Cyclization of propionic acid (VII) (0.14 g, 0.38 mmol) with TFAA (0.30 g) in dichloromethane (20 ml) afforded [4](1,1′)[4](2,2′)-α-oxo[3](4,4′)ferrocenophane (VIII) (0.13 g, quant.), which was recrystallized from hexane to give orange-yellow prisms, m.p. 152—156°C. (Found: M^+, 348.1175. $C_{21}H_{24}OFe$ calcd.: mol. wt., 348.1175.) IR spectrum (KBr): 1665 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.88, 2.25 and 2.38 (8 H, 4 H and 4 H, each m, —CH_2— of (1,1′)- and (2,2′)- bridges), 2.83 (4 H, s, —CH_2— of (4,4′)-bridge), 4.48 (2 H, s, 3,5-H), 4.68 (2 H, s, 3′,5′-H). Mass spectrum: 348 (M^+, 100), 320 ([M — CO]$^+$, 12).

[4](1,1′)[4](2,2′)[4](4,4′)Ferrocenophane (X)

Bridge enlargement of [4][4][3]ferrocenophane (VIII) (50 mg, 0.14 mmol) in benzene (10 ml)/methanol (50 ml) with diazomethane in ether (50 ml) gave [4](1,1′)[4](2,2′)-α-oxo[4](4,4′)- and [4](1,1′)[4](2,2′)-β-oxo[4](4,4′)ferrocenophanes (IXa: 1.4 mg, 2.7%; IXb: 40 mg, 79%). Recrystallization of α-ketone IXa from hexane gave yellow plates, m.p. 120—122°C. (Found: M^+, 362.1314. $C_{22}H_{26}OFe$ calcd.: mol. wt., 362.1331.) IR spectrum (KBr): 1640 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.80—2.60 (22 H, m, —CH_2—), 3.87 (2 H, s, 3,5-H), 4.46 (2 H, s, 3′,5′-H). Mass spectrum: 362 (M^+, 100), 308 ([M — COC_2H_2]$^+$, 13).

β-Ketone IXb was recrystallized from hexane to give orange-yellow needles, m.p. 110—112°C. (Found: M^+, 362.1341. $C_{22}H_{26}OFe$ calcd.: mol. wt., 362.1331.) IR spectrum (KBr): 1695 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.85 and 2.30 (each 8 H, m, —CH_2— of (1,1′)- and (2,2′)-bridges), 2.71 (4 H, s, —CH_2— at γ and δ-positions of (4,4′)bridge), 3.21 (2 H, s, isolated —CH_2— at α-position), 3.97 and 4.01 (each 2 H, s, Cp-H). Mass spectrum: 362 (M^+, 100), 334 ([M — CO]$^+$, 10).

Reduction of β-ketone IXb (20 mg, 0.06 mmol) with $LiAlH_4$ (6 mg)/$AlCl_3$(15 mg) in dry ether (10 ml) gave [4](1,1′)[4](2,2′)[4](4,4′)ferrocenophane (X) (13 mg, 68%), which was identical to that derived from formylferrocenophane (XI) [3] by comparison of melting points and spectra.

[4](1,1′)-α-Oxo[3](2,2′)[4](3,3′)ferrocenophane (XV)

Ethyl bromoacetate (0.69 g, 4.0 mmol) was added to a stirred suspension of 2-formyl[4](1,1′)[4](3,3′)ferrocenophane (XII) (0.67 g, 2.1 mmol) [3], zinc (0.50 g) and a small amount of iodine in absolute benzene(10 ml)/ether(2 ml) in an N_2 atmosphere. After refluxing for 10 min, water was added to the cooled

reaction mixture. Extracts with benzene were washed with 6 *N* HCl and then with saturated aq. NaCl, dried over Na_2SO_4, and evaporated. The residue was column-chromatographed over alumina to give 2-(2-ethoxycarbonylvinyl)[4]-(1,1′)[4](3,3′)ferrocenophane (XIII) (0.66 g, 84%) as a deep red oil. (Found: M^+, 392.1419. $C_{23}H_{28}O_2Fe$ calcd.: mol. wt., 392.1436.) IR spectrum (neat liq.): 1710 and 1625 [ν(C=O)] and ν(C=C)]. ^{1}H NMR spectrum ($CDCl_3$): 1.34 and 4.23 (3 H and 2 H, t and q, respectively, —CH_2CH_3), 1.44—2.77 (16 H, m, —CH_2—), 3.80—3.92 (3 H, m, 2′,4′,5′-H), 4.19 (2 H, s, 4,5-H), 6.07 and 7.84 (each 1 H, an AB system, J = 16, =CH—). Mass spectrum: 392 (M^+, 100), 364 ([$M - C_2H_4$]$^+$, 8), 319 ([$M - CO_2C_2H_5$]$^+$, 5).

Catalytic hydrogenation of the acrylate XIII (0.65 g, 1.7 mmol) in ethanol (50 ml) with 10% Pd-C gave 2-(2-ethoxycarbonylethyl)ferrocenophane (XIV) (0.60 g, 92%), a yellow oil. (Found: M^+, 394.1589. $C_{23}H_{30}O_2Fe$ calcd.: mol. wt., 394.1593.) IR spectrum (neat liq.): 1735 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.25 and 4.10 (3 H and 2 H, t and q, respectively, —CH_2CH_3), 1.56—2.94 (20 H, m, —CH_2—), 3.65 (1 H, t, J = 1.4, 2′-H), 3.89 (2 H, d, J = 1.4, 4′,5′-H), 3.91 (2 H, s, 4,5-H). Mass spectrum: 394 (M^+, 100), 366 ([$M - C_2H_4$]$^+$, 5), 293 ([$M - C_2H_4CO_2C_2H_5$]$^+$, 12).

A solution of propionate XIV (0.40 g, 1.0 mmol) in ethanol (20 ml) and 20% aq. NaOH (20 ml) was stirred for 10 min at 80°C. The reaction mixture was neutralized with dil. HCl and extracted with dichloromethane. The extracts were washed with saturated aq. NaCl, dried over $CaCl_2$ and concentrated to 10 ml under a reduced pressure. Polyphosphate ester (PPE) (5 ml) was added to the above concentrated solution in dichloromethane and the mixture was stirred on an oil bath at 80°C for 10 min. Water was added to the cooled reaction mixture, and the hydrolysate was neutralized with saturated aq. $NaHCO_3$ containing ascorbic acid, and extracted with benzene. The extracts were washed with saturated aq. NaCl, dried over $CaCl_2$ and evaporated. The resulting residue was chromatographed over preparative scale thin layer of silica gel with benzene/ethyl acetate (30/1) as a developing solvent. The second band of seven yielded [4](1,1′)-α-oxo[3](2,2′)[4](3,3′)ferrocenophane (XV) (0.10 g, 28% from XIV) as the main product. Recrystallization of XV from benzene/hexane gave red prisms, m.p. 136—138°C. (Found: C, 72.41; H, 7.05; M^+, 348.1189. $C_{21}H_{24}OFe$ calcd.: C, 72.42; H, 6.95%; mol. wt., 348.1175.) IR spectrum (KBr): 1645 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.80—3.36 (20 H, m, —CH_2—), 3.86 (2 H, s, 4,5-H), 4.12 (2 H, s, 4′,5′-H). Mass spectrum: 348 (M^+, 100), 320 ([$M - CO$]$^+$, 4).

[4](1,1′)[3](2,2′)[4](3,3′)Ferrocenophane (XVI)

Reduction of [4]-α-oxo[3][4]ferrocenophane (XV) (35 mg, 0.10 mmol) in ether(5 ml)/benzene(2 ml) with $LiAlH_4$(8 mg)/$AlCl_3$ (27 mg) at room temperature for 3 h gave two products, which were separated from each other by column chromatography over silica gel. The band eluted with hexane/ethyl acetate (20/1) yielded [4](1,1′)[3](2,2′)[4](3,3′)ferrocenophane (XVI) (14 mg, 42%), which was recrystallized from hexane to give yellow needles, m.p. 128—131°C. (Found: M^+, 334.1363. $C_{21}H_{26}Fe$ calcd.: mol. wt., 334.1382.) ^{1}H NMR spectrum ($CDCl_3$): 1.60—2.54 (22 H, m, —CH_2—), 3.90 (4 H, s, Cp-H). Mass spectrum: 334 (M^+, 100), 278 ([$M - C_4H_8$]$^+$, 6).

The incomplete reduction product, [4](1,1′)-α-hydroxy[3](2,2′)[4](3,3′)-ferrocenophane (XVII) (14 mg, 41%) eluted with ethyl acetate, was identified by high-resolution mass and IR spectroscopy.

[4](1,1′)[4](2,2′)[4](3,3′)Ferrocenophane (XIX)

Bridge enlargement of [4]-α-oxo[3][4]ferrocenophane (XV) (46 mg, 0.13 mmol) in benzene (3 ml) in the presence of $BF_3 \cdot OEt_2$ (0.025 ml, 0.20 mmol) with diazomethane gave [4]-α-oxo-[4]-β-oxo-[4][4]ferrocenophanes and the starting material, which were separated from each other by preparative TLC over silica gel with benzene as developing solvent. The starting material (16 mg, 34%) was recovered from the second band. The first band yielded [4](1,1′)-β-oxo-[4](2,2′)[4](3,3′)ferrocenophane (XVIIIb) (22 mg, 45%), which was recrystallized from hexane to give orange-yellow prisms, m.p. 165—168°C. (Found: C, 73.40; H, 7.49; M^+, 362.1346. $C_{22}H_{26}OFe$: C, 72.90; H, 7.23%; mol. wt., 362.1332.) IR spectrum: 1700 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.55—3.15 (20 H, m, $-CH_2-$), 3.29 (2 H, s, isolated $-CH_2-$), 3.91 (2 H, s, 4,5-H), 3.97 (2 H, s, 4′,5′-H). Mass spectrum: 362 (M^+, 100), 334 ([M — CO]$^+$, 15).

The third band yielded [4](1,1′)-α-oxo[4](2,2′)[4](3,3′)ferrocenophane (XVIIIa) (5 mg, 11%), which was recrystallized from hexane to give orange-yellow prisms, m.p. 190—193°C. (Found: M^+, 362.1324. $C_{22}H_{26}OFe$ calcd.: mol. wt., 362.1332.) IR spectrum (KBr): 1655 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$); 1.64—3.06 (22 H, m, $-CH_2-$), 3.95 (2 H, s, 4,5-H), 4.19 (2 H, s, 4′,5′-H). Mass spectrum: 362 (M^+, 100), 334 ([M — CO]$^+$, 5).

Reduction of [4]-β-oxo[4][4]ferrocenophane (XVIIIb) (6.1 mg, 0.017 mmol) in ether(2 ml)/benzene(1 ml) with $LiAlH_4$(1.3 mg)/$AlCl_3$(4.7 mg) at room temperature for 5 h resulted in the production of two compounds. The first band eluted with hexane/ethyl acetate (20/1) in column chromatography over silica gel yielded [4](1,1′)[4](2,2′)[4](3,3′)ferrocenophane (XIX) (3.3 mg, 55%), which was recrystallized from hexane to give yellow plates, m.p. 166—169°C. (Found: M^+, 348.1526. $C_{22}H_{28}Fe$ calcd.: mol. wt., 348.1539.) ^{1}H NMR spectrum ($CDCl_3$): 1.66—2.64 (24 H, m, $-CH_2-$), 3.88 (4 H, s, Cp H). ^{13}C NMR spectrum ($CDCl_3$); 26.460, 27.289 and 27.678 (methylene C), 66.760 (4,5,4′,5′-C), 83.718 (2,2′-C), 85.422 (1,3,1′,3′-C). Mass spectrum: 348 (M^+, 100).

The more polar product eluted with ethyl acetate was confirmed to be [4](1,1′)-β-hydroxy[4](2,2′)[4](3,3′)ferrocenophane (XX) (2.6 mg, 43%) by spectroscopic means.

Diethyl-α-oxo[3]ferrocenophanes (XXVI and XXVII)

Formylation of 1,1′-diethylferrocene (XXI) [13] (17.1 g, 0.07 mol) with DMF(10.2 g, 0.14 mol)/$POCl_3$(21.5 g, 0.14 mol) gave two isomeric formylated diethylferrocenes, which were separated by column chromatography over silica gel. The first band eluted with hexane/ethyl acetate (30/1) yielded 2,1′-diethyl-1-formylferrocene (XXII) (2.98 g, 16%) as a dark red oil. IR spectrum (neat liq.): 1675 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.09 and 1.18 (each 3 H, t, $-CH_3$), 2.24 and 2.62 (each 2 H, q, $-CH_2-$), 4.03 (4 H, s, unformylated Cp H), 4.36 and 4.57 (2 H and 1 H, an ABX system, formylated Cp H), 9.92 (1 H, s, —CHO).

The second band yielded 3,1′-diethyl-1-formylferrocene (XXIII) (9.01 g, 47%) as a dark red oil. (Found: M^+, 270.0683. $C_{15}H_{18}OFe$: mol. wt., 270.0705.) IR spectrum (neat liq.): 1670 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$); 1.12 and 1.20 (each 3 H, t, —CH_3), 2.27 and 2.41 (each 2 H, q, —CH_2—), 4.08 (4 H, s, unformylated Cp H), 4.44 and 4.61 (1 H and 2 H, an ABX system, formylated Cp H), 9.83 (1 H, s, —CHO). Mass spectrum: 270 (M^+, 100), 241 ([M — CHO]$^+$, 16), 226 ([M — CHO — CH_3]$^+$, 14), 212 ([M — CHO — CH_2CH_3]$^+$, 17).

Condensation of XXIII (9.01 g, 33 mmol) with malonic acid (6.86 g, 66 mmol) quantitatively gave 3,1′-diethyl-1-(2-carboxyvinyl)ferrocene (XXIV) (10.3 g) as a dark red oil. (Found: M^+, 312.0824. $C_{17}H_{20}O_2Fe$ calcd.: mol. wt., 312.0812.) IR spectrum (neat liq.): 1673 and 1614 [ν(C=O) and ν(C=C)]. ^{1}H NMR spectrum ($CDCl_3$): 1.13 and 1.18 (each 3 H, t, —CH_3), 2.26 and 2.38 (each 2 H, t, —CH_2—), 3.97 and 4.32 (4 H and 3 H, bs, Cp H), 5.93 and 6.59 (each 2 H, an AX system, J = 15, =CH—), 9.88 (1 H, bs, —COOH). Mass spectrum: 312 (M^+, 100).

Catalytic hydrogenation of XXIV (8.90 g, 29 mmol) with Pd-C quantitatively gave 3,1′-diethyl-1-(2-carboxyethyl)ferrocene (XXV) (9.10 g) as a yellow oil. (Found: M^+, 314.0987. $C_{17}H_{22}O_2Fe$ calcd.: mol. wt., 314.0968.) IR spectrum (neat liq.): 1707 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.14 and 1.15 (each 3 H, t, —CH_3), 2.29 and 2.33 (each 2 H, q, —CH_2— of ethyl group), 2.60, (4 H, bs, —CH_2— of propionic acid moiety), 3.88 and 3.94 (4 H and 3 H, s and m, respectively, Cp H), 10.04 (1 H, bs, —COOH). Mass spectrum: 314 (M^+, 100).

Cyclization of XXV (8.25 g, 26 mmol) with TFAA (14.30 g, 68 mmol) afforded cyclization products, which were separated into two components by column chromatography over silica gel. The first band eluted with hexane/ethyl acetate (30/1) yielded a mixture (1/1) of 3,2′- and 3,5′-diethyl-α-oxo[3](1,1′)-ferrocenophanes (XXVIIa and XXVIIb) (1.32 g, 17%), as a dark red oil. (Found: M^+, 296.0865. $C_{17}H_{20}OFe$ calcd.: mol. wt., 296.0862.) IR spectrum (neat liq.): 1670 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$); 1.09, 1.12 and 1.22 (6 H, an intensity ratio of 1/1/2, each t, —CH_3), 2.19 (2 H, q, —CH_2— of ethyl group), 2.35—2.70 (2 H, m, —CH_2— of ethyl group), 2.80—2.95 and 3.20—3.60 (each 2 H, m, —CH_2— of bridge), 3.93, 3.99, 4.05, 4.26, 4.46 and 4.53 (3 H, 1 H, 2 H, 2 H, 1 H and 1 H, m, Cp H), 4.78 and 4.92 (each 1 H, dd, J = 1.5, 2.6, 5′-H of XXVIIa and 2′-H of XXVIIb). Mass spectrum: 296 (M^+, 100).

The second band eluted with hexane/ethyl acetate (30/1) yielded a mixture (1/3) of 3,3′- and 3,4′-diethyl-α-oxo[3](1,1′)ferrocenophanes (XXVIa and XXVIb) (4.62 g, 60%) as a dark red oil. (Found: M^+, 296.0839. $C_{17}H_{20}OFe$ calcd.: mol. wt.: 296.0862.) IR spectrum (neat liq.): 1670 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$): 1.03 and 1.10 (each t, —CH_3 of XXVIa), 1.12 and 1.19 (each t, —CH_3 of XXVIb), 2.06 and 2.07 (each q, —CH_2— of XXVIa), 2.18 and 2.30 (each q, —CH_2— of XXVIb), 2.88 (s, —CH_2— of bridge), 3.74 and 4.10 (each dd, J = 1.5, 2.6, 4,5-H of XXVIb), 3.89 and 4.26 (each dd, J = 1.5, 2.6, 4,5-H of XXVIa), 4.40—4.80 (m, other Cp H). Mass spectrum: 296 (M^+, 100), 281 ([M — CH_3]$^+$, 6).

Bridge enlargement of diethyl-α-oxo[3]ferrocenophanes (XXVI)

Treatment of a mixture of 3,3′- and 3,4′-diethyl-α-oxo[3](1,1′)ferrocenophanes (XXVIa and XXVIb) with diazomethane in the presence of methanol or

$BF_3 \cdot OEt_2$ gave isomeric α-ketone (XXVIII) and β-ketone (XXIX) (8 and 78%, or 13 and 26%, respectively). The first band eluted with hexane/ethyl acetate (20/1) in column chromatography over silica gel yielded a mixture of 3,3′- and 3,4′-diethyl-β-oxo[4]ferrocenophanes (XXIX) as a yellow oil. (Found: M^+, 310.1009. $C_{18}H_{22}OFe$ calcd.: mol. wt., 310.1018.) IR spectrum (neat liq.): 1695 [ν(C=O)]. ^1H NMR spectrum ($CDCl_3$): 1.06 and 1.12 (6 H, each t, $-CH_3$), 2.11 and 2.30 (4 H, each q, $-CH_2-$ of ethyl groups), 2.73 (4 H, s, $-CH_2-$ of bridge), 3.26 (2 H, s, isolated $-CH_2-$ of bridge), 3.66—4.12 (6 H, m, Cp H). Mass spectrum: 310 (M^+, 100) 282 ([$M - CO$]$^+$, 19).

The second band yielded a mixture of 3,3′- and 3,4′-diethyl-α-oxo[4]ferrocenophane (XXVIII) as a yellow oil. (Found: M^+, 310.1009. $C_{18}H_{22}OFe$ calcd.: mol. wt., 310.1018.) IR spectrum (neat liq.): 1640 [ν(C=O)]. ^1H NMR spectrum ($CDCl_3$): 0.96—1.32 (6 H, m, $-CH_3$), 2.00—2.62 (10 H, m, $-CH_2-$), 3.76—4.62 (6 H, m, Cp H). Mass spectrum: 310 (M^+, 100), 282 ([$M - CO$]$^+$, 10).

Bridge enlargement of [4](1,1′)[4](3,3′)-α-oxo[3](4,5′)ferrocenophane (XXXIII)

Bridge enlargement of [4][4]-α-oxo[3](4,5′)ferrocenophane (XXXIII) (70 mg, 0.20 mmol) with diazomethane in the presence of $BF_3 \cdot OEt_2$ gave isomeric α- and β-ketones XXXIVa and XXXIVb and the starting material. The first band in the preparative TLC over silica gel with benzene/ethyl acetate (30/1) as developing solvent yielded [4](1,1′)[4](3,3′)-β-oxo[4](4,5′)ferrocenophane (XXXIVb) (7 mg, 10%), which was recrystallized from hexane to give yellow prisms, m.p. 177—179°C. (Found: M^+, 362.1352. $C_{22}H_{26}OFe$ calcd.: mol. wt., 362.1332.) IR spectrum (KBr): 1685 [ν(C=O)]. ^1H NMR spectrum ($CDCl_3$): 1.10—3.10 (20 H, m, $-CH_2-$), 3.20 and 3.57 (each 1 H, an AB system, $J = 12$, isolated $-CH_2-$), 3.96 (2 H, m, 2,2′-H), 4.03 (1 H, d, $J = 1.5$, 5-H), 4.10 (1 H, d, $J = 1.5$, 4′-H). Mass spectrum: 362 (M^+, 100), 334 ([$M - CO$]$^+$, 34).

The starting material (XXXIII) (34 mg, 49%) was recovered from the second band. The third band in the column chromatography yielded [4](1,1′)[4](3,3′)-α-oxo[4](4,5′)-ferrocenophane (XXXIVa) (15 mg, 20%), which was recrystallized from hexane to give orange-yellow prisms, m.p. 158—160°C. (Found: C, 73.12; H, 7.15; M^+, 362.1353. $C_{22}H_{26}OFe$ calcd.: C, 72.90; H, 7.23%; mol. wt., 362.1332.) IR spectrum (KBr): 1630 [ν(C=O)]. ^1H NMR spectrum ($CDCl_3$): 1.16—3.44 (22 H, m, $-CH_2-$), 3.73 (1 H, d, $J = 1.5$, 2-H), 3.95 (1 H, d, $J = 1.5$, 5-H), 4.35 (1 H, d, $J = 1.5$, 2′-H), 4.55 (1 H, d, $J = 1.5$, 4′-H). Mass spectrum: 362 (M^+, 100), 334 ([$M - CO$]$^+$, 32).

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