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The Synthesis and Stereochemistry of 2,3-Ferrocenocyclopentenone

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An optical isomer of 2,3-ferrocenocyclopentenone (X) has been synthesized from methyl (1*S*) (−)-2-hydroxymethylferrocenecarboxylate *via* a six-step synthesis. The absolute configuration of (−)-X has been confirmed by a comparison of its CD and ORD curves with those of the corresponding ferrocene homologs previously recorded. The mass spectrum of X is also discussed.

The asymmetric induction achieved in the lithiation of (*S*)(+)-(*N*-α-pipecolylmethyl)ferrocene (I)[1] has opened a synthetic route to chiral 1,2-disubstituted ferrocene derivatives, such as methyl (1*S*)(−)-2-hydroxymethylferrocenecarboxylate (III). Schlögl and his co-workers have established the absolute configuration of ferrocene derivatives in their study of ferrocene chirality.[2] They prepared 2,3-ferrocenocyclohexenone and several substituted 2,3-ferrocenocyclopentenones, but not the parent compound (X). The conventional

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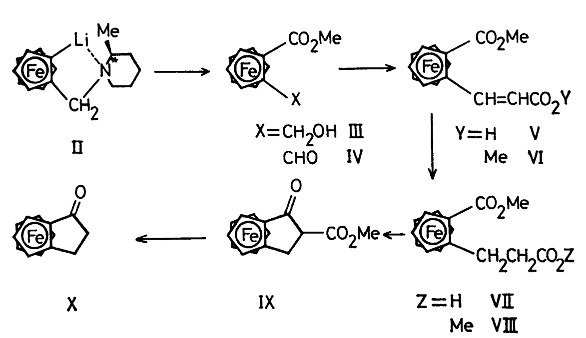
[1] T. Aratani, T. Gonda, and H. Nozaki, *Tetrahedron* **26**, 5453 (1970).

[2] a) H. Lehner and K. Schlögl, *Monatsh. Chem.*, **102**, 277 (1971); b) H. Falk and K. Schlögl, *ibid.*, **102**, 33 (1971); c) H. Falk, H. Lehner, and K. Schlögl, *ibid.*, **101**, 967 (1970); d) H. Falk and O. Hofer, *ibid.*, **100**, 1540 (1969); e) H. Falk, O. Hofer, and K. Schlögl, *ibid.*, **100**, 624 (1969); f) H. Falk and K. Schlögl, *ibid.*, **96**, 266, 1065 (1965); g) K. Schlögl, M. Fried, and H. Falk, *ibid.*, **95**, 576 (1964).

cyclization of ferrocenylpropionic acid preferentially gives the heteroannularly-bridged ketone.[3,4] We now wish to report on a successful synthetic approach to this ketone (X) in its optically-active form (*cf.* Scheme 1).



Scheme 1

The oxidation of (1*S*)(—)-III with MnO_2 gave methyl (—)-2-formylferrocenecarboxylate (IV). The subsequent Knoevenagel-Doebner condensation of the aldehyde (—)-(IV) with malonic acid gave the acid (—)-V. The catalytic hydrogenation of (—)-V with PtO_2, followed by esterification with diazomethane, afforded the diester (—)-VIII. The Dieckmann-type cyclization of the diester (—)-VIII with NaH in tetrahydrofuran gave the *β*-ketoester (IX),[5] which was then treated with dilute KOH to furnish the ketone (—)-X.

The ORD and CD curves of (—)-VI, (—)-VIII, and (—)-X were very similar to those of (1*S*)(—)-III of a known configuration,[1] as is shown in Figs. 1 and 2. Thus, every product obtained in each step of this synthetic route possesses the (1*S*,2*R*)-configuration.

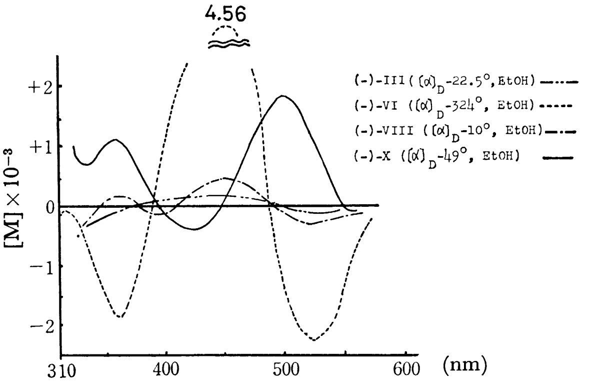


Fig. 1. ORD of III, VI, VIII, and X.

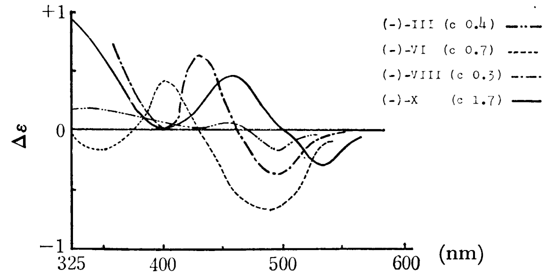


Fig. 2. CD of III, VI, VIII, and X (EtOH).

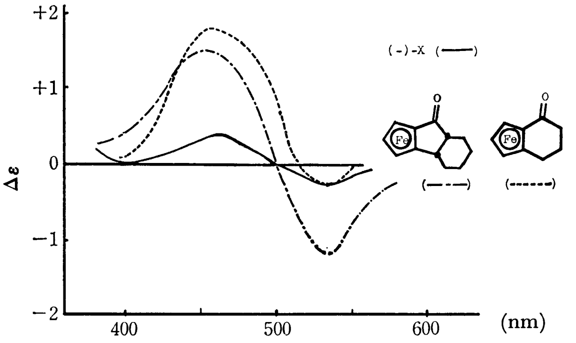
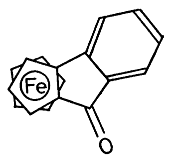
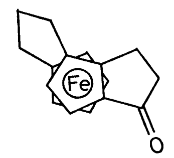


Fig. 3. CD of (—)-X and its homologs so far reported.

Furthermore, the CD curve of (—)-X in the region of the 300—600 nm ferrocene band area was similar to that of the ferrocenocyclohexenone of the (1*S*)-configuration[2g] and had the opposite sign of those of the substituted ferrocenocyclopentenones of the (1*R*)-configuration[2a,d,e] (see the following Scheme and Fig. 3).



CD value:
Δε —3.50 (485 nm, EtOH)



CD value:
Δε —1.30 (490 nm, EtOH)

On the basis of these facts, it was confirmed that the absolute configuration of (—)-X is (1*S*,2*R*).[6]

Finally, it should be added that the mass spectrum of the ketone (X) now synthesized exhibited an intense peak at *m/e* 212. The exact mass of this peak (212.027) showed that decarbonylation had occurred instead of the loss of ethylene.[8] The cleavage accounts for the metastable peak at *m/e* 187 (see Fig. 4).

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[3] a) B. Gantheron and J. C. LeBlanc, *Bull. Soc. Chim. France*, **1971**, 3629; b) B. Gantheron, J. C. LeBlanc, and C. Moise, *C. R. Acad. Sci., Ser. C*, **271**, 1394 (1970); c) M. Rosenblum, A. K. Banerjee, N. Danieli, R. W. Fish, and V. Schlatter, *J. Amer. Chem. Soc.*, **85**, 316 (1963); d) K. L. Rinehart, Jr., R. J. Curby, Jr., D. H. Gustafson, K. G. Harbison, R. E. Bozak, and D. E. Bublitz, *ibid.*, **84**, 3263 (1962); e) E. A. Hill and J. H. Richards, *ibid.*, **83**, 4216 (1961); f) J. W. Huffman and D. J. Raff, *J. Org. Chem.*, **26**, 3588 (1961).

[4] In the cyclization of substituted ferrocenylpropionic acids, the homoannularly-bridged ketones have occasionally been obtained as minor products. See Refs. 3a and 3b.

[5] a) J. D. Hobson, J. Raines, and R. J. Whiteoak, *J. Chem, Soc.*, **1963**, 3495; b) W. Mock and J. H. Richards, *J. Org. Chem.*, **27**, 4050 (1962).

[6] The thermolysis of the tosylhydrazone sodium salt of (—)-X in pyridine,[7] and the dehydration of the corresponding alcohol of (—)-X with acidic Al_2O_3,[2] were attempted, but neither gave any of the expected cyclopentadiene.

[7] a) A. Sonoda and I. Moritani, *J. Organometal. Chem.*, **26**, 133 (1971); b) A. Sonoda, I. Moritani, S. Yasuda, and T. Wada, *Tetrahedron*, **26**, 3075 (1970); c) A. Sonoda and I. Moritani, This Bulletin, **43**, 3522 (1970).

[8] This result is coincident with the fragmentation of 1-indanone (90% decarbonylation, 10% loss of ethylene). See: J. H. Bowie, *Aust. J. Chem.*, **19**, 1619 (1966).

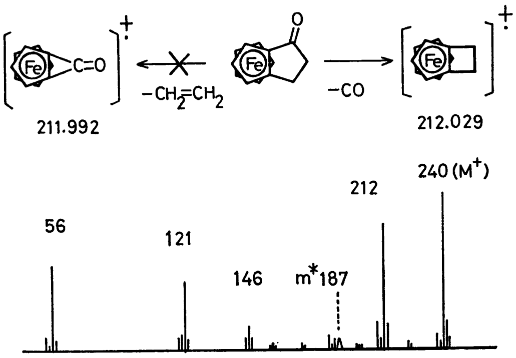

Fig. 4. Mass spectrum of ketone X.

Experimental

All the melting points and the boiling points are uncorrected. The microanalyses were performed at the Elemental Analyses Center of Kyoto University. The IR spectra were recorded on a Shimadzu IR-27-G spectrophotometer, and the mass spectra, on a Hitachi RMU-6L spectrometer. The NMR spectra were taken in a CDCl$_3$ or CCl$_4$ solution at 60 MHz on a JEOL C-60-H spectrometer; the chemical shifts are given in ppm from a TMS internal standard. The NMR signals are designated as *s* for a singlet, *d* as a doublet, *t* as a triplet, and *m* as a multiplet. The optical rotations were measured using a cell 1 or 5 cm in length at room temperature (20°C), and *c* is given in g/100 m*l*. The ORD and CD spectra were recorded on a JASCO ORD-5 spectropolarimeter in a EtOH solution (*c* in mg/m*l*), with a cell 1 cm long. The UV spectra were taken in EtOH on a Hitachi EPS-2 recording spectrophotometer. Column chromatography was carried out on Sumitomo activated alumina unless otherwise stated. The purity of every product was checked on tlc (Merck Aluminiumoxid G).

*(*S*) (+)-(*N-*α-Pipecolylmethyl)ferrocene (I).* The optical resolution of α-pipecoline was performed by fractional recrystallizations of its hydrogen tartrate from water.[9] A mixture of (*S*) (+)-α-pipecoline ($[\alpha]_D$ +32.0° (neat) (*i.e.*, 89% optical purity based on the reported value 36.0°), 96.9 g, 980 mmol) and (dimethylaminomethyl)ferrocene methiodide (74.8 g, 200 mmol) in water (70 m*l*) was stirred under refluxing (120°C) for 65 hr. Work-up, followed by distillation, gave (*S*) (+)-I as a dark red oil (61.3 g, 96%); bp 147—150°C/0.3 mmHg; $[\alpha]_D$ +69.1° (*c* 2.1, EtOH). The IR and NMR spectra were superimposable on those of an authentic sample.[1]

*Methyl (*1S*) (−)-2-Hydroxymethylferrocenecarboxylate (III).* The lithiation of the amine (+)-I ($[\alpha]_D$ +69.1° (EtOH), 36.3 g, 130 mmol) with *n*-BuLi, followed by carbonation, gave a lithium salt of the amino acid.[1] The treatment of the lithium salt with an excess of methyl iodide in methanol gave a crude methiodide (124 g), which was subsequently heated under reflux for 25 hr with aqueous KOH (10%, 600 m*l*). The resulting product was esterified with diazomethane to afford (*1S*) (−)-III ($[\alpha]_D$ −22.5° (*c* 5.5, CHCl$_3$), 8.0 g, 23%). This alcohol was identified by comparison with an authentic sample (IR, NMR).[1]

*Preparation of Methyl (*1S*) (−)-2-(β-Methoxycarbonylvinyl)-ferrocenecarboxylate (VI).* A mixture of the alcohol (1*S*) (−)-III ($[\alpha]_D$ −22.5°, 8.0 g, 29 mmol) and dry, active MnO$_2$ (35 g, 400 mmol) in chloroform was stirred under reflux in a nitrogen atmosphere for 2 hr. The subsequent filtration from an inorganic solid and the evaporation of the filtrate gave the aldehyde (*1S*) (−)-IV ($[\alpha]_D$ −384° (*c* 0.60, EtOH), 7.9 g 99%). IR (neat): 1710, 1670, 1290, 1275, 1220, 1190, 1160, 1150, 1080, 1035, 1005, 825, 805, and 750 cm^{-1}. NMR (CDCl$_3$, 10%); δ 10.68 (s, 1H, -CHO), 5.15 (m, 2H), 4.78 (m, 1H), 4.33 (s, 5H, cyclopentadienyl ring protons), and 3.88 (s, 3H, -CO$_2$Me). The semicarbazone was prepared as usual and was recrystallized from chloroform; mp 210°C (decomp.).

Found: C, 50.6; H, 4.6; N, 12.5%. Calcd for $C_{14}H_{15}FeO_3N_3$: C, 51.1; H, 4.6; N, 12.8%.

A mixture of the aldehyde ($[\alpha]_D$ −384°, 7.9 g, 29 mmol), malonic acid (5.4 g, 52 mmol), and piperidine (20 drops) dissolved in pyridine (130 m*l*) was heated under reflux (90—100°C) in a nitrogen atmosphere for 1.5 hr. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in chloroform. After the solution had been washed with aqueous phosphoric acid, the acidic product was extracted with excess aqueous NaOH. The aqueous layer was acidified with aqueous phosphoric acid and extracted with ether–chloroform to give the (1*S*) (−)-acid, V ($[\alpha]_D$ −520° (*c* 0.10, acetone), 2.0 g, 22% based on the starting amount of III), which was sufficiently pure for a further reaction. The esterifcation of V with diazomethane, followed by column chromatography (benzene elution), gave VI as dark red needles; ($[\alpha]_D$ −324° (*c* 0.56, EtOH), mp 92.5—94°C (from EtOH). IR (KBr): 1710, 1695, 1627, 1273, 1250, 1220, 1190, 1155, 1083, 1030, 1015, 992, 940, 850, and 812 cm^{-1}. NMR (CDCl$_3$, 5%): δ 8.37 (*d*, 1H, -CH=), 6.15 (*d*, 1H, -CH=), 5.00, 4.80, 4.60 (m, 3H) and 4.20 (s, 5H, cyclopentadienyl ring protons), and 3.80, 3.85 (s, 6H, -CO$_2$Me). ORD (*c* 0.7): $[M]_{520}$ −2280°, $[M]_{490}$ 0°, $[M]_{446}$+4560°, $[M]_{384}$ 0°, $[M]_{368}$−1930°, $[M]_{324}$ 0°, $[M]_{300}$−300°.

Found: C, 58.9; H, 5.1%. Calcd for $C_{16}H_{16}FeO_4$: C, 58.6; H, 4.9%.

*Preparation of Methyl (*1S*) (−)-2-(β-Methoxycarbonylethyl)-ferrocenecarboxylate (VIII).* A mixture of the acid V ($[\alpha]_D$ −520°, 0.30 g, 1.0 mmol), PtO$_2$ (0.03 g), and ethanol was stirred under a hydrogen atmosphere at room temperature for 12 hr. A usual work-up, followed by column chromatography (ethanol elution), gave VII as fine, yellow-orange crystals; ($[\alpha]_D$ 0°, $[\alpha]_{545}$ −25.0° (*c* 4.5, EtOH), 0.27 g, 90%). The saturated acid, VII, was esterified with diazomethane in water–benzene–ether (1 : 1 : 1 ratio). Column chromatography (benzene elution) gave fine, yellow-orange crystals; diester VIII ($[\alpha]_D$ −10° (*c* 0.56, EtOH), 0.25 g, 90%), mp 66.5—68°C (from EtOH). IR (Nujol): 1730, 1715, 1305, 1290, 1257, 1215, 1193, 1175, 1138, 1105, 1030, 818, and 780 cm^{-1}. NMR (CDCl$_3$, 10%): δ 4.73 (m, 1H), 4.28 (m, 2H), 4.13 (s, 5H, cyclopentadienyl ring protons), 3.79, 3.15 (s, 6H, -CO$_2$Me), and 3.30—2.85, 2.65—2.35 (m, 4H, methylenes). ORD (*c* 0.3): $[M]_{524}$ −270°, $[M]_{494}$ 0°, $[M]_{454}$ +540°, $[M]_{418}$ 0°, $[M]_{400}$ −216°, $[M]_{384}$ 0°, $[M]_{364}$ +270°, $[M]_{350}$ 0°, $[M]_{296}$ −620° and $[M]_{260}$ 0°.

Found: C, 58.4; H, 5.6%. Calcd for $C_{16}H_{18}FeO_4$: C, 58.2; H, 5.5%.

*Cyclization of VIII to (*1S*) (−)-2,3-ferrocenocyclopentenone (X).* A mixture of VIII ($[\alpha]_D$ −10°, 0.33 g, 1.0 mmol) and NaH (50%) (0.20 g, 4.0 mmol) in dry tetrahydrofuran (25 m*l*) was stirred under reflux in a nitrogen atmosphere for 7 hr.[5] After cooling, methanol (10 m*l*) was added to the reaction mixture. Acidification with aqueous hydrochloric acid, followed by ether extraction, gave the crude β-ketoester, IX (0.20 g, 70%).

The product, IX (0.20 g, 0.7 mmol), dissolved in tetra-

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[9] W. Marckwald, *Ber.* **29**, 43 (1896); b) W. Leithe, *Monatsh. Chem.*, **50**, 40 (1932).

hydrofuran–benzene (1:2) (15 m*l*), was heated with aqueous NaOH (4%, 5 m*l*) for 5 hr under reflux in a nitrogen atmosphere. After cooling, the dark red benzene layer was separated from the aqueous tetrahydrofuran layer, and then benzene (10 m*l*) was added to the aqueous tetrahydrofuran layer in the reaction vessel. The mixture was again refluxed. This operation was repeated until no dark red color appeared in the new benzene layer. The combined benzene layers were then washed with water, and dried (Na_2SO_4). Column chromatography (benzene elution) gave X as dark red crystals; ($[\alpha]_D$ −49° (*c* 0.32, EtOH), 0.10 g, 60%), mp 82—83°C (from MeOH). IR (KBr): 1685, 1300, 1255, 1230, 1194, 1100, 1082, 1039, 999, 838, 827, and 815 cm^{-1}. NMR ($CDCl_3$, 7%): δ 4.57 (m, 3H), 4.12 (s, 5H, cyclopentadienyl ring protons), and 2.83 (*m*, 4H, methylenes). MS (relative abundance): *m/e* 240 (100), 212 (80), 186 (9), 184 (9), 146 (14), 121 (41), and 56 (60). ORD (*c* 1.7): $[M]_{580}$ −16°, $[M]_{564}$ −83°, $[M]_{550}$ 0°, $[M]_{494}$ +1849°, $[M]_{448}$ 0°, $[M]_{428}$ −414°, $[M]_{398}$ 0°, $[M]_{362}$ +1242°, $[M]_{341}$ +662°, $[M]_{305}$ +2070°, $[M]_{284}$ +1242°, $[M]_{230}$ +2484°. λ_{max} (EtOH): 465 nm (log, ε 2.39), 328 nm (log ε 2.84).

Found: C, 65.1; H, 5.1%. Calcd for $C_{13}H_{12}FeO$: C, 65.0; H, 5.0%.

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