Pergamon

Tetrahedron, Vol. 52, No. 4, pp. 1461-1472, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00972-8

Addition of Silyl Enol Ethers and Silyl Ketene Acetals to Ferrocenylmethyl Ethers. Synthesis of Precursors to Chiral Bridged Ferrocenophanes

Andrew J. Locke, Nicolas Gouti, Christopher J. Richards*, David E. Hibbs and Michael B. Hursthouse

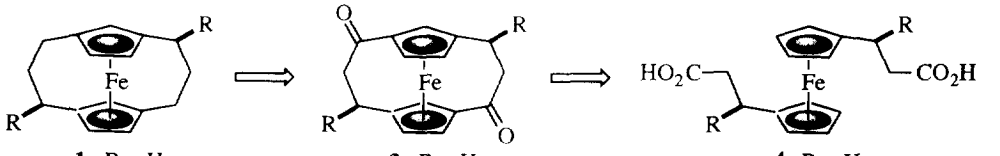
Department of Chemistry, University of Wales, Cardiff, PO Box 912, Cardiff, CF1 3TB, UK.

Abstract: Ferrocenylmethyl methyl ethers react cleanly with silyl enol ethers and silyl ketene acetals promoted by $BF_3.OEt_2$ to give β-ferrocenylcarbonyl adducts in excellent yields. Silyl enol ethers react with up to 3 : 1 selectivity for the *anti* diastereoisomer. Meso 1,1'-bis(α-hydroxybenzyl)ferrocene reacts with methanol and acetic acid to give exclusively meso 1,1'-bis(α-methoxybenzyl)ferrocene. Both this and the corresponding racemic diastereoisomer may be separated by recrystallisations of an initially 1:1 mixture. Racemic and meso 1,1'-bis(α-methoxybenzyl)ferrocenes react with 1-ethoxy-1-(trimethylsilyloxy)ethene promoted by $BF_3.OEt_2$ to give racemic and meso β-ferrocene adducts with retention of relative configuration as determined by an X-ray crystal structure analysis of the corresponding meso 1,1'-diacid obtained on hydrolysis.

Introduction

We are interested in the design of structures that contain a metal redox centre lying within a pronounced chiral environment, as such frameworks would provide a novel basis for the synthesis of catalysts and metallo-enzyme mimetics. To this end it was noted that bridged ferrocenophanes contain an iron redox centre at the heart of a conformationally restricted molecule due to reduced rotation of the linked cyclopentadienyl rings. Of the many examples known, [3](1,1')[3](3,3')ferrocenophane **1** is attractive as it contains non-equivalent open and closed approaches to the iron, and introduction of substituents at R (*e.g.* **2** R = Ph) utilises the C_2-symmetry of the molecule to place the open side of the ferrocenophane within a chiral pseudo-helical environment.

The parent ferrocenophane **1** has previously been synthesised *via* reduction of the diketone **3** obtained by cyclisation of the 1,1'-diacid **4** (Scheme 1).[1] To use this approach for the synthesis of **2** and **5** requires introduction of the correct stereochemistry in the key 1,1'-disubstituted intermediate rac-**6**, before addressing the regioselectivity and diastereoselectivity of the final ring closures.



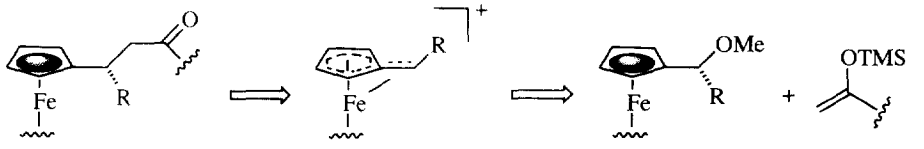
1 R = H
2 R = Ph

3 R = H
5 R = Ph

4 R = H
rac-**6** R = Ph

Scheme 1

In our approach to the synthesis of the general unit **7** we decided to re-examine the reaction of silyl enol ethers and silyl ketene acetals with α-ferrocenylcarbenium ions **8** generated *in situ* (Scheme 2). It has previously been reported that 1-acetoxy-1-ferrocenylethane reacts with enoxysilanes in the presence of ZnI_2 to give **7** (R = Me),[2] and we have described the reaction of isolated α-ferrocenylcarbenium ions **8** with silyl enol ethers.[3] However, due to the anticipated difficulty of isolating 1,1'- derivatives of reactive acetoxyferrocenes and α-ferrocenylcarbenium ions, we decided to examine the reactions of stable ferrocenylmethyl methyl ethers **9**. In this paper we describe the reaction of enoxysilanes with **9**, report on the stereochemistry of these processes, and their application to the synthesis of rac-**6** and the corresponding diastereoisomer meso-**6**.



7 **8** **9**

Scheme 2

Results and discussion

Addition of a slight excess of $BF_3.OEt_2$ to a CH_2Cl_2 solution of ferrocenylmethyl ether **10** and (*Z*)-silyl enol ether **11** cooled in an acetone/cardice bath, followed by warming of the reaction mixture to room temperature, led to the isolation of the corresponding addition product **12** in excellent yield (Table 1, entry 1). In order to examine the stereoselectivity of this reaction, the α-methyl ether **13** was combined with **11** under the same conditions resulting in a 3 : 1 ratio of diastereomeric products (entry 2). Recrystallisation gave a pure sample of the major diastereoisomer **14** and this was shown to have the *anti* configuration (as defined by the arrangement of substituents about the ferrocene to carbonyl backbone) by an X-ray crystal structure analysis (Figure 1).[4]

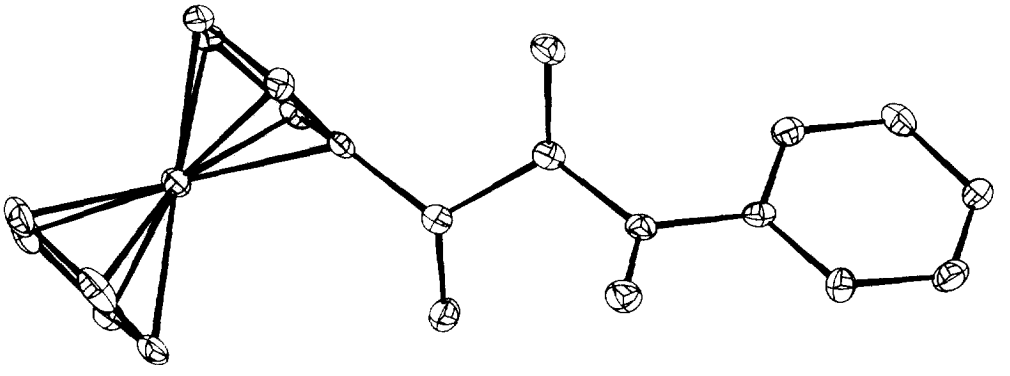
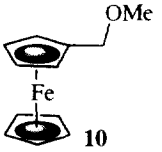
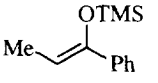
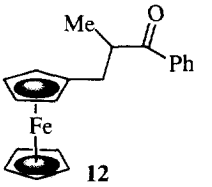
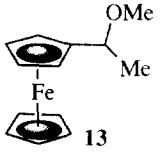
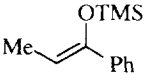
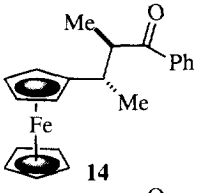
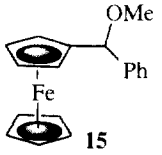
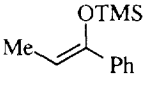
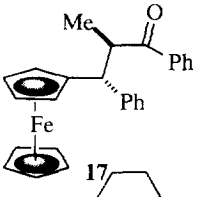
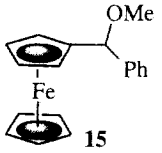
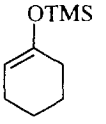
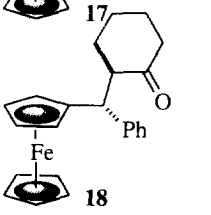
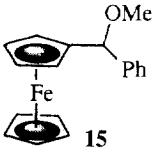
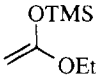
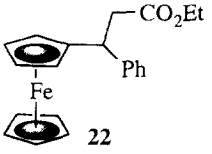
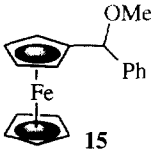
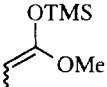
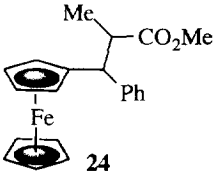
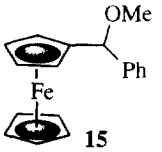
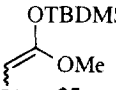
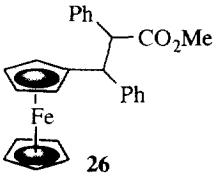
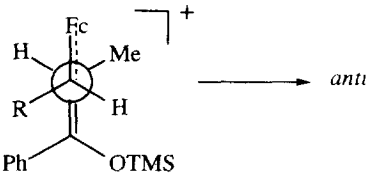


Figure 1. Molecular structure of **14**

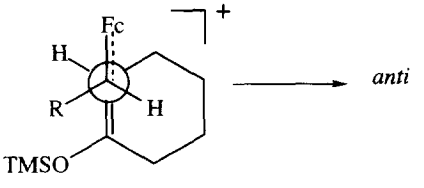
Table 1

Entry	Substrate	Enoxysilane	Product (major isomer)	Ratio of isomers	Yield (%)
1	 **10**	 **11**	 **12**	–	92
2	 **13**	 **11**	 **14**	3 : 1	91
3	 **15**	 **11**	 **17**	3.2 : 1	80
4	 **15**	 **16**	 **18**	2.7 : 1	87
5	 **15**	 **21**	 **22**	–	64
6	 **15**	 **23**	 **24**	1.5 : 1	78
7	 **15**	 **25**	 **26**	2 : 1	72

The α-phenyl ether **15** reacted to give a similar ratio of diastereoisomers with both **11** (entry 3) and the (*E*)-silyl enol ether **16** derived from cyclohexanone (entry 4). In both cases the corresponding major products, **17** and **18** respectively, were isolated as pure diastereoisomers after column chromatography and/or recrystallisation. Their *anti* configurations were revealed by comparison of their spectral data with that of samples for which we have previously published X-ray structural analyses.[3] It is assumed that these reactions proceed by BF_3 promoted elimination of methoxide followed by rapid addition of the silyl enol ether to the resultant α-ferrocenylcarbenium ion. This is supported by similarities in the *anti*/*syn* ratios to those obtained when the α-ferrocenylcarbenium ions are first isolated.[3] Use of Lewis acids other than $BF_3.OEt_2$ made almost no change to the ratio of diastereoisomers obtained. The *anti* selectivity may be accounted for by the transition state representations **19** and **20** for the (*Z*)- and (*E*)-silyl enol ethers respectively, in which the donor and acceptor systems themselves adopt an *anti* relationship.



19



20

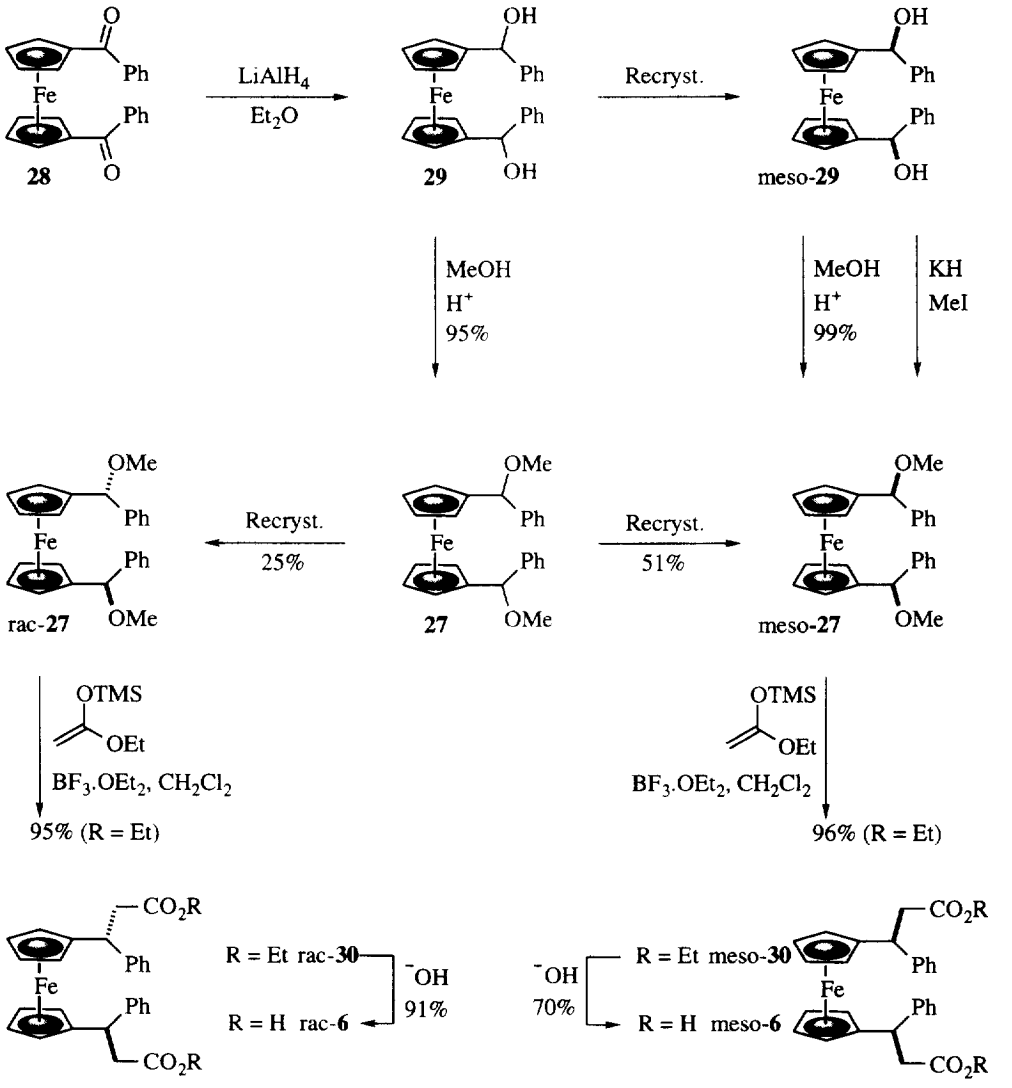
In contrast, dicobalt hexacarbonyl complexed propargylic ethers were found to give *syn* alkylated products with silyl enol ethers in the presence of a Lewis acid.[5] These reactions are proposed to proceed *via* the intermediacy of a carbenium ion which adopts a *gauche* relationship with the donor silyl enol ether leading to a predominance of *syn* diastereoisomers, the most common outcome from the combination of two prochiral π-systems.[6] The difference in selectivity between the two organometallic systems may reflect the greater bulk of ferrocene favouring an extended *anti* transition state in which steric repulsions are minimised.

In order to gain access to β-ferrocenylpropanoic acids for ferrocenophane synthesis, the reaction was extended to silyl ketene acetals. Combining **15** with **21** promoted by $BF_3.OEt_2$ in CH_2Cl_2 as before, resulted in a good yield of the β-ferrocenyl ester **22** (Table 1, entry 5). The stereoselectivity of silyl ketene acetal addition was investigated initially with **23** (*E*/*Z* = 5 : 1) which gave a 1.5 : 1 ratio of diastereoisomers **24** (entry 6). Use of silyl ketene acetal **25** (*E*/*Z* = 8 : 1) containing a bulkier phenyl substituent gave only a 2 : 1 ratio of isomers **26**. These ratios precluded isolation and determination of the major diastereoisomers, so both **24** and **26** were characterised as mixtures.

To extend this method to include the synthesis of **6** required the corresponding 1,1'-bis ethers **27** which proved easy to obtain by the route outlined in Scheme 3. 1.1'-Dibenzoylferrocene **28** was reduced with $LiAlH_4$ in Et_2O to give a 1 : 1 ratio of meso and racemic diol diastereoisomers **29**. Two recrystallisations yielded a single diastereoisomer having a m.p. and ^1H NMR data similar to that reported for material previously described as the racemate.[7] However, doubts over this assignment have arisen[8] and so we obtained an X-ray crystal structure analysis which revealed the single diastereoisomer to be meso-**29** (Figure 2).[9]

It was also reported[7] that the other diastereoisomer, now known to be rac-**29**, could not be isolated diastereomerically pure despite repeated recrystallisations. Thus the 1 : 1 ratio of diols **29** were treated with acetic acid in methanol to give a 1 : 1 ratio of methyl ethers **27**. Three recrystallistions were sufficient to yield

golden yellow plates of a single diastereoisomer (51% recovery), as revealed by ^{1}H NMR spectroscopy. This material proved to be meso-**27** as treatment of meso-**29** with methyl iodide and potassium hydride in THF, conditions which are not expected to affect the integrity of the stereocentres, gave material with an identical ^{1}H NMR spectrum to that of the crystals obtained by repeated recrystallisation. Treatment of the diol meso-**29** with 10% acetic acid in methanol also gave meso-**27**, with no signals in the ^{1}H NMR spectrum of the reaction mixture due to rac-**27**. In addition, methanolysis under the same conditions of a 2 : 1 ratio of meso/rac-**29** gave an identical ratio of meso/rac-**27** revealing that methanolysis of both diols proceeds with retention of relative stereochemistry.



Scheme 3

The mother liquors obtained from the first recrystallisation of 1 : 1 meso/rac-**27** were evaporated and repeatedly recrystallised to give pure rac-**27** (25% recovery). Treatment of this material with four equivalents of silyl ketene acetal **21** and two equivalents of $BF_3.OEt_2$ in CH_2Cl_2 cooled in an acetone/cardice bath, followed by warming the reaction mixture to room temperature, led to the isolation in excellent yield of a double addition product **30**. Repartition of this reaction with meso-**27** also proceeded in excellent yield. Examination of the crude ^1H NMR spectra of the two reaction mixtures revealed that both products were pure diastereoisomers, *i.e.* a number of peaks in one spectrum were not observed in the other, and visa versa. Both diesters **30** were hydrolysed to their corresponding diacids without difficulty, and as before ^1H NMR spectroscopy was used to confirm that both diacids were pure diastereoisomers. An X-ray crystal structure analysis of one of the diacids showed it to be meso-**6** (Figure 3),[10] and as this material had been obtained from meso-**27** this X-ray structure revealed that BF_3 promoted silyl ketene acetal addition to meso- and rac-**27** proceeded with retention of relative configuration in both cases.

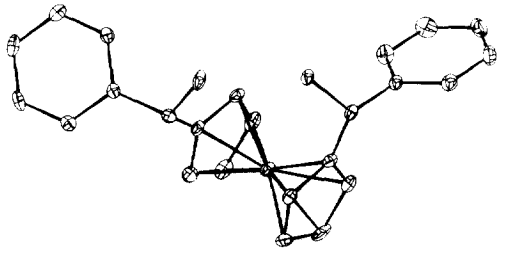


Figure 2. Molecular structure of meso-**29**

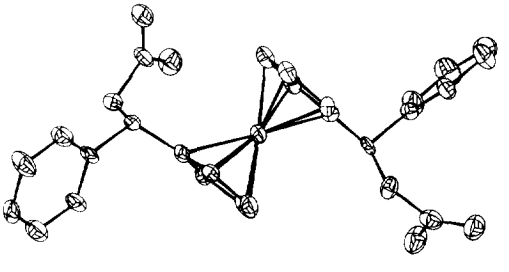


Figure 3. Molecular structure of meso-**6**

Substitution of the α-position of monosubstituted ferrocenes proceeds *via* stereospecific elimination of the leaving group away from iron, and addition of the nucleophile along the same trajectory resulting in overall retention of configuration.[11] That both methylation and silyl ketene acetal addition proceed with retention of relative configuration reveals that there is no epimerisation of intermediate α-ferrocenylcarbenium ions under both sets of reaction conditions. It is assumed that these reactions occur stepwise as dissolution of **29** in CF_3CO_2D at room temperature results in formation of the monocation as previously shown by ^1H NMR spectroscopy, and formation of the dication requires the use of DSO_3F at -70 °C.[8] In addition, during methylation and addition of the first silyl ketene acetal to **27,** there is the possibility that the initially formed α-ferrocenylcarbenium ion is trapped by the remaining hydroxy or methoxy group to form a cyclic oxonium intermediate, which is subsequently opened by nucleophilic addition to either α-carbon.

In summary, we have demonstrated that ferrocenylmethyl ethers react cleanly with silyl enol ethers and silyl ketene acatals promoted by $BF_3.OEt_2$. Both (*E*)- and (*Z*)-silyl enol ethers give moderate *anti* selectivity with appropriate substituted ferrocenylmethyl ethers, silyl ketene acetals resulting in lower selectivity. The

reaction also works well with 1,1'-bis ethers, proceeding with retention of relative stereochemistry and providing a synthesis of diastereomerically pure substituted 1,1'-propanoic acids. We are currently investigating the asymmetric version of this reaction and the use of meso- and rac-**6** for the synthesis of novel ferrocenophanes.

Experimental

Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl and dichloromethane from calcium hydride. Petroleum ether refers to that fraction boiling in the range 40-60 °C and hexane to the fraction boiling in the range 65.5-70 °C. Column chromatography was performed on SiO_2 (40-63 μm). Melting points were determined on a Gallenkamp digital melting point apparatus and a Kofler hot stage, and are not corrected. Elemental analyses were performed on a Perkin Elmer 240C Elemental Analyser. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer. NMR spectra were recorded on a Bruker AMX 360 (360 MHz ^1H and 90 MHz ^{13}C) spectrometer. Mass spectra were recorded on a Fisons VG Platform II. Ferrocenylmethyl ethers **10**, **13** and **15** were prepared by treatment of the corresponding alcohols with MeOH/AcOH.[12] Silyl enol ethers **11**[13] and **16**,[13] silyl ketene acetals **21**[14], **23**[14] and **25**[15], and 1,1'-bis(α-hydroxybenzyl)ferrocenes **29**[7] were prepared as previously described.

General method for addition of silyl enol ethers or silyl ketene acetals to monosubstituted ferrocenylmethyl ethers. Synthesis of **12**, **14**, **17**, **18**, **22**, **24** *and* **26**.

The appropriate ferrocenylmethyl ether (0.5 mmol) and silyl enol ether or silyl ketene acetal* (1.0 mmol) were dissolved in dry CH_2Cl_2 (5 ml) and cooled to -78 °C under an atmosphere of nitrogen. To the resulting solution was added dropwise $BF_3.OEt_2$ (0.55 mmol) and the reaction mixture stirred at -78 °C for 15 min. The cooling bath was removed, the reaction warmed to room temperature and quenched with saturated $NaHCO_3$(aq) (10 ml). The two layers were separated and the aqueous layer washed with additional CH_2Cl_2 (10 ml). The combined organics were dried (Na_2SO_4), filtered, evaporated *in vacuo* and the residue column chromatographed. Where appropriate, a small portion of the reaction mixture was examined by ^1H NMR spectroscopy before chromatography to check the ratio diastereoisomers obtained. Yields refer to material isolated after chromatography.

*__21__ used as a 1 : 1 mixture with $TMSCH_2CO_2Et$[14]

3-Ferrocenyl-2-methylpropiophenone **12**

Chromatography with 1 : 19 EtOAc/petroleum ether gave **12** (92%) as a yellow crystalline solid.

m.p. 64 - 65 °C (EtOAc/hexane) (Found: C, 72.02; H, 5.99. $C_{20}H_{20}FeO$ requires C, 72.31; H, 6.07%); ν_{max} (nujol) 1682 cm^{-1} (C=O); δ_H ($CDCl_3$) 1.15 (3 H, d, *J* 6.9, -C*H*$_3$), 2.45 (1 H, dd, *J* 14.1, 7.3, -C*H*HCHCH$_3$-), 2.90 (1 H, dd, *J* 14.1, 6.4, -CH*H*CHCH$_3$-), 3.49 (1 H, hextet, *J* 6.9, -CH$_2$C*H*CH$_3$-), 3.99 - 4.08 (4 H, m, Fc), 4.07 (5 H, s, C$_5$*H*$_5$), 7.43 (2 H, t, *J* 7, Ph - *meta*), 7.53 (1 H, t, *J* 7, Ph - *para*), 7.89 (2 H, d, *J* 7, Ph - *ortho*); δ_C {^1H} ($CDCl_3$) 17.70 (-*C*H$_3$), 34.01 (-*C*H$_2$CHCH$_3$-), 43.26 (-CH$_2$*C*HCH$_3$-), 67.37 (Fc), 67.57 (Fc), 68.59 (*C*$_5$H$_5$), 68.76 (Fc), 69.12 (Fc), 86.32 (Fc - *ipso*), 128.27 (Ph), 128.57 (Ph), 132.81 (Ph - *para*), 136.54 (Ph - *ipso*), 203.87 (*C*=O); *m/z* (EI) 332 (M^+, 75%), 267 (59), 223 (52), 199 (78), 135 (60), 121 (94), 77 (69), 56 (100).

(2 R, 3 S*)-3-Ferrocenyl-2-methylbutyrophenone* **14**

Chromatography with 1 : 9 EtOAc/petroleum ether gave a yellow crystalline solid (91%) isolated as a 3 : 1 mixture of isomers. Recrystallisation from EtOAc/petroleum ether gave pure **14**.

m.p. 112 - 113 °C (Found: C, 72.60; H, 6.20. $C_{21}H_{22}FeO$ requires C, 72.85; H, 6.40%); ν_{max} (nujol) 1669 cm^{-1} (C=O); δ_H ($CDCl_3$) 0.96 (3 H, d, *J* 6.9, -C*H*$_3$), 1.33 (3 H, d, *J* 6.9, -C*H*$_3$), 2.92 (1 H, quintet, *J* 7, FcC*H*CH$_3$-), 3.27 (1 H, quintet, *J* 7, -C*H*CH$_3$COPh), 3.98 (1 H, brs, Fc), 4.04 - 4.10 (3 H, m, Fc), 4.09 (5 H, s, C$_5$*H*$_5$), 7.44 (2 H, t, *J* 7, Ph - *meta*), 7.54 (1 H, t, *J* 7, Ph - *para*), 7.89 (2 H, d, *J* 7, Ph - *ortho*); δ_C {^{1}H} ($CDCl_3$) 15.94 (-*C*H$_3$), 19.14 (-*C*H$_3$), 36.47 (FcCHCH$_3$-), 48.17 (-CHCH$_3$COPh), 65.70 (Fc), 66.83 (Fc), 67.14 (Fc), 68.46 (*C*$_5$H$_5$), 69.30 (Fc), 92.31 (Fc - *ipso*), 128.25 (Ph), 128.55 (Ph), 132.77 (Ph - *para*), 137.29 (Ph - *ipso*), 204.36 (*C*=O); *m/z* (EI) 346 (M^+, 63%), 213 (100), 121 (62), 77 (31), 56 (31).

(2 R, 3 R*)-3-Ferrocenyl-3-phenyl-2-methylpropiophenone* **17**

Chromatography with 1 : 9 EtOAc/petroleum ether gave a yellow crystalline solid (80%) isolated as a 3.2 : 1 mixture of isomers. Recrystallisation from EtOAc gave pure **17**.

m.p. 162.5 - 163 °C (Found: C, 76.23; H, 5.88. $C_{26}H_{24}FeO$ requires C, 76.48; H, 5.92%); ν_{max} (nujol) 1672 cm^{-1} (C=O); δ_H ($CDCl_3$) 1.08 (3 H, d, *J* 6.4, -C*H*$_3$), 3.75 (5 H, s, C$_5$*H*$_5$), 3.88 - 3.95 (2 H, m, -C*H*PhC*H*CH$_3$-), 4.06 (1 H, brs, Fc), 4.13 (2 H, brs, Fc), 4.21 (1 H, brs, Fc), 7.12 (1 H, t, *J* 7, Ph - *para*), 7.23 (2 H, t, *J* 7, Ph - *meta*), 7.35 (2 H, d, *J* 7, Ph - *ortho*), 7.36 (2 H, t, *J* 7, Ph - *meta*), 7.46 (1 H, t, *J* 7, Ph - *para*), 7.74 (2 H, d, *J* 7, Ph - *ortho*); δ_C {^{1}H} ($CDCl_3$) 17.69 (-*C*H$_3$), 48.27 and 48.79 (-*C*HPh*C*HCH$_3$-), 66.48 (Fc x 2), 68.16 (Fc), 68.53 (*C*$_5$H$_5$), 70.38 (Fc), 90.86 (Fc - *ipso*), 126.27 (Ph - *para*), 127.89 (Ph), 127.93 (Ph), 128.34 (Ph), 128.50 (Ph), 132.58 (Ph - *para*), 136.96 (Ph - *ipso*), 144.05 (Ph - *ipso*), 203.77 (*C*=O); *m/z* (EI) 408 (M^+, 45%), 275 (100), 121 (45), 77 (32), 56 (23), 44 (62).

(R)-2-[(R*)-ferrocenylphenylmethyl]cyclohexanone* **18**

Chromatography with 1 : 9 EtOAc/petroleum ether gave a yellow crystalline solid (87%) isolated initially as a 2.7 : 1 mixture of isomers. These could be separated by careful chromatography with the same solvent mixture. Fractions containing the major isomer were combined and recrystallised from EtOAc/petroleum ether to give pure **18**.

m.p. 102.5 - 103.5 °C (Found: C, 74.32; H, 6.63. $C_{23}H_{24}FeO$ requires C, 74.20; H, 6.50%); ν_{max} (nujol) 1708 cm^{-1} (C=O); δ_H ($CDCl_3$) 1.37 - 2.00 (6 H, m, -(C*H*$_2$)$_3$-), 2.17 (1 H, td, *J* 12, 6, -C*H*HCO-), 2.29 (1 H, dt, *J* 13, 5, -CH*H*CO-), 2.84 (1 H, td, *J* 9, 5, FcCHPhC*H*-), 3.80 (5 H, s, C$_5$*H*$_5$), 3.97 (1 H, d, *J* 9, FcC*H*Ph-), 4.01 (1 H, brs, Fc), 4.12 (3 H, brs, Fc), 7.22 (1 H, t, *J* 7, Ph - *para*), 7.32 - 7.39 (4 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 24.43 (-*C*H$_2$-), 28.65 (-*C*H$_2$-), 32.78 (-*C*H$_2$-), 42.27, 44.83, 58.14, 66.40 (Fc), 66.69 (Fc), 67.94 (Fc), 68.52 (*C*$_5$H$_5$), 70.10 (Fc), 90.80 (Fc - *ipso*), 126.28 (Ph - *para*), 127.90 (Ph), 128.64 (Ph), 144.55 (Ph - *ipso*), 211.93 (*C*=O); 372 (M^+, 57%), 275 (100), 121 (73), 56 (29).

Ethyl 3-ferrocenyl-3-phenylpropanoate **22**

Chromatography with 3 : 97 EtOAc/petroleum ether gave **22** (64%) isolated as an orange oil

(Found: C, 69.98; H, 6.47. $C_{21}H_{22}FeO_2$ requires C, 69.63; H, 6.12%); ν_{max} (liquid) 1732 cm^{-1} (C=O); δ_H ($CDCl_3$) 1.13 (3 H, t, *J* 7.1, -C*H*$_3$), 2.85 (1 H, dd, *J* 15.1, 10.3, -C*H*HCO$_2$Et), 3.11 (1 H, dd, *J* 15.1, 4.9, -CH*H*CO$_2$Et), 3.99 (1 H, brs, Fc), 4.05 (2 H, qd, *J* 7.1, 2.1, -C*H*$_2$CH$_3$), 4.07 - 4.13 (3 H, m, Fc) 4.10 (5 H, s, C$_5$*H*$_5$), 4.23 (1 H, dd, *J* 10.4, 4.8, FcC*H*Ph-), 7.16 - 7.29 (5 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 14.08 (-*C*H$_3$), 42.13 (FcCHPh-), 42.21 (-*C*H$_2$CO$_2$Et), 60.32 (-OCH$_2$CH$_3$), 66.58 (Fc), 67.21 (Fc), 67.72 (Fc), 67.75 (Fc), 68.64

(C_5H_5), 92.68 (Fc - *ipso*), 126.49 (Ph -*para*), 127.66 (Ph), 128.21 (Ph), 144.03 (Ph - *ipso*), 171.97 (*C*=O); *m/z* (EI) 362 (M^+, 100%), 275 (35), 153 (28) 121 (62).

Methyl 3-ferrocenyl-3-phenyl-2-methylpropanoate **24**

Chromatography with 1 : 9 EtOAc/petroleum ether gave **24** (78%) as an orange oil isolated as a 1.5 : 1 mixture of isomers.

(Found: C, 69.45; H, 6.27. $C_{21}H_{22}FeO_2$ requires C, 69.63; H, 6.12%); ν_{max} (liquid) 1737 cm^{-1} (C=O); δ_H ($CDCl_3$) 0.94* (3 H, d, *J* 6.9, -CHC*H*$_3$-), 1.09$ (3 H, d, *J* 6.9, -CHC*H*$_3$-), 2.78 - 2.86$ (1 H, m, -C*H*CH$_3$-), 2.87 - 2.94* (1 H, m, -C*H*CH$_3$-), 3.36$ (3 H, s, -OC*H*$_3$), 3.57* (3 H, s, -OC*H*$_3$), 3.64 (1 H, d, *J* 10.6, FcC*H*Ph-) 3.76 (5H, s, C_5H_5), 3.80 (1 H, d, *J* 10.2, FcC*H*Ph-), 3.83 (5 H, s, C_5H_5), 3.98 (1 H, brs, Fc), 4.02 (1 H, brs, Fc), 4.06 (3 H, brs, Fc), 4.10 (2 H, brs, Fc), 4.17 (1 H, brs, Fc), 7.21 - 7.39 (10 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 16.64 and 16.71 (-CH*C*H$_3$-), 47.50, 47.66, 49.61, 49.73, 51.21 and 51.45 (Fc*C*HPh*C*HCH$_3$- and -O*C*H$_3$), 66.55 (Fc), 66.95 (Fc), 67.06 (Fc), 68.11 (Fc), 68.31 (Fc), 68.69 (C_5H_5), 70.24 (Fc), 90.53 and 91.08 (Fc - *ipso*), 126.55 and 126.67 (Ph - *para*), 127.89 (Ph), 128.17 (Ph), 128.38 (Ph), 128.65 (Ph), 142.13 and 143.55 (Ph - *ipso*), 175.90 and 176.41 (*C*=O); *m/z* (EI) 362 (M^+, 100%), 275 (85), 153 (38), 121 (88), 59 (51), 56 (42).

*Major diastereoisomer. $Minor diastereoisomer.

Methyl 3-ferrocenyl-2,3-diphenylpropanoate **26**

Chromatography with 1 : 9 EtOAc/petroleum ether gave **26** (72%) as an orange solid isolated as a 2 : 1 mixture of isomers.

(Found: C, 73.77; H, 5.98. $C_{26}H_{24}FeO_2$ requires C, 73.60; H, 5.70%); ν_{max} (nujol) 1735 cm^{-1} (C=O); δ_H ($CDCl_3$) 3.34$ (3 H, s, -OC*H*$_3$), 3.54* (3 H, s, -OC*H*$_3$), 3.75$ (5 H, s, C_5H_5), 3.83* (5 H, s, C_5H_5), 4.00* (1 H, d, *J* 11.7, -C*H*Ph-), 4.04* (1 H, brs, Fc), 4.10* (2 H, brs, Fc), 4.21* (1 H, brs, Fc), 4.36* (1 H, d, *J* 11.7, -C*H*Ph-), 7.04 - 7.47 (20 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 49.64*, 50.58$, 51.60$, 51.84*, 59.73$ and 59.90* (Fc*C*HPh*C*HPhCO- and -O*C*H$_3$), 66.51$ (Fc), 66.67$ (Fc), 66.83* (Fc), 66.94* (Fc), 67.57$ (Fc), 68.05* (Fc), 68.39$ (C_5H_5), 68.61* (C_5H_5), 69.13* (Fc), 69.59$ (Fc), 89.69$ (Fc - *ipso*), 90.83* (Fc - *ipso*), 126.28 (Ph), 126.75 (Ph), 126.94 (Ph), 127.08 (Ph), 127.39 (Ph), 127.75 (Ph), 128.02 (Ph), 128.21 (Ph), 128.60 (Ph x 2), 128.89 (Ph), 129.22 (Ph), 137.24* (Ph - *ipso*), 137.47$ (Ph - *ipso*), 141.46* (Ph - *ipso*), 142.55$ (Ph - *ipso*), 172.81$ (C=O), 173.72* (C=O); *m/z* (EI), 424 (M^+, 41%), 275 (86), 121 (100), 56 (32).

*Major diastereoisomer. $Minor diastereoisomer.

Methylation of 1,1'-bis(α-hydroxybenzyl)ferrocenes **29**. *Preparation and separation of meso and racemic 1,1'-bis(α-methoxybenzyl)ferrocenes* **27**.

A 1 : 1 mixture of meso and racemic 1,1'-bis(α-hydroxybenzyl)ferrocenes **29** (20.0 g, 50.2 mmol) were dissolved in methanol (200 ml). To the resultant yellow solution was added glacial acetic acid (10 ml) and the reaction stirred at room temperature overnight. After this time the reaction mixture, which contained a large amount of yellow crystalline material, was carefully quenched with saturated $NaHCO_3$(aq.) (50 ml) and extracted with Et_2O (200 ml). The aqueous phase was further extracted with Et_2O (100 ml), the combined organics phases dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give 20.24 g (95%) of a yellow crystalline solid, a 1 : 1 mixture of meso- and rac-**27**.

For the following description, A = EtOAc, B = petroleum ether. Recrystallisation of 28.34 g of this 1 : 1 mixture from 2 : 1 A/B (225 ml) gave 11.4 g of crystals as a 10 : 1 mixture. Further recrystallisation from the same solvent mixture (150 ml) gave 8.7 g of crystals that were again recrystallised from 100 ml of 2 : 1 A/B to give pure meso-**27** as golden yellow plates (7.2 g, 51%). The mother liquors from the first recrystallisation

were evaporated to give an approximately 4 : 1 mixture of racemic and meso diastereoisomers. This mixture was subject to the following series of recrystallisations: i) 2 : 1 A/B (70 ml) to give 9.43 g as a 8 : 1 ratio, ii) 1.25/1 A/B (30 ml) to give 7.14 g as a 12 : 1 mixture, iii) 1 : 1.25 A/B (45 ml) to give 5.70 g also as a 12 : 1 mixture. Pure rac-**27** was obtained as a yellow fibrous solid after an additional four recrystallisations from 1 : 1 A/B (approx. 1 g to 6 ml of solvent mixture), yield = 3.50 g (25%).

(R)-(S)-1, 1'-bis(α-methoxybenzyl)ferrocene, meso-**27**

m.p. 138.5 - 140.5 °C (Found: C, 73.05; H, 6.33. $C_{26}H_{26}FeO_2$ requires C, 73.25; H, 6.15%); ν_{max} (nujol) 1065 cm^{-1} (C-O); δ_H ($CDCl_3$) 3.24 (6 H, s, -OC*H*$_3$), 3.85 (2 H, brs, Fc), 3.91 (2 H, brs, Fc), 4.01 (2 H, brs, Fc), 4.13 (2 H, brs, Fc), 4.85 (2 H, s, -C*H*Ph-), 7.25 - 7.40 (10 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 56.78 (-O*C*H$_3$), 67.84 (Fc) 68.75 (Fc x 3), 82.43 (-*C*HPh-), 90.27 (Fc - *ipso*), 127.37 (Ph), 127.62 (Ph - *para*), 128.16 (Ph), 141.35 (Ph - *ipso*); *m/z* (EI) 426 (M^+, 84%), 212 (63), 153 (100).

(R)-(R*)-1, 1'-bis(α-Methoxybenzyl)ferrocene*, rac-**27**

m.p. 104 - 106 °C (Found: C, 73.19; H, 6.19. $C_{26}H_{26}FeO_2$ requires C, 73.25; H, 6.15%); ν_{max} (nujol) 1065 cm^{-1} (C-O); δ_H ($CDCl_3$) 3.21 (6 H, s, -OC*H*$_3$), 3.76 (2 H, brs, Fc), 3.92 (2 H, brs, Fc), 3.97 (2 H, brs, Fc), 4.20 (2 H, brs, Fc), 4.82 (2 H, s, -C*H*Ph-), 7.25 - 7.38 (10 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 56.85 (-O*C*H$_3$), 67.97 (Fc) 68.53 (Fc), 68.82 (Fc), 68.91 (Fc), 82.51 (-*C*HPh-), 90.48 (Fc - *ipso*), 127.40 (Ph), 127.68 (Ph - *para*), 128.27 (Ph), 141.60 (Ph - *ipso*); *m/z* (EI) 426 (M^+, 100%), 212 (86), 153 (93).

Conversion of (R)-(S)-1, 1'-bis(α-hydroxybenzyl)ferrocene (meso-**29**) *into (R)-(S)-1, 1'-bis(α-methoxybenzyl)ferrocene* (meso-**27**)

Method A. A solution of sodium hydride (60% in mineral oil, 0.16 g, 4 mmol) in THF (10 ml) was cooled in an ice bath and to this mixture was added methyl iodide (0.57 g, 4 mmol). After further addition of a solution of meso-**29** (0.398 g, 1 mmol) in THF (4 ml), the resulting mixture was stirred and allowed to warm to room temperature overnight, and then quenched with saturated $NaHCO_3$(aq) (15 ml). The two layers were separated and the aqueous phase extracted with Et_2O (10 ml), the organics combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow residue. A ^{1}H NMR spectrum of this product revealed no peaks corresponding to rac-**27**.

Method B. Meso-**29** (0.057 g, 0.14 mmol) was dissolved in methanol (10 ml) and glacial acetic acid (1 ml) and the reaction mixture stirred at room temperature overnight. The reaction was worked up as described above to give meso-**27** (0.060 g, 99%). No rac-**27** could be detected in this product by ^{1}H NMR spectroscopy.

Addition of silyl ketene acetal **21** *to 1, 1'-bis(α-methoxybenzyl)ferrocenes* rac- *and* meso-**27**. *Synthesis of (R*)-(R*)- and (R)-(S)-1,1'-bis(3-[ethyl 3-phenylpropanoate])ferrocenes* rac- *and* meso-**30**

Silyl ketene acetal **21*** (3.10 g, 9.7 mmol of **21**) and rac-**27** (1.013 g, 2.38 mmol) were dissolved in dry CH_2Cl_2 (15 ml) and cooled to -78 °C under an atmosphere of nitrogen. To the resulting solution was added dropwise $BF_3.OEt_2$ (0.71 g, 5.0 mmol) and the reaction mixture stirred at -78 °C for 15 min. The cooling bath was removed, the reaction allowed to warm to room temperature and then quenched with saturated $NaHCO_3$(aq) (15 ml). The two layers were separated and the aqueous layer washed with additional CH_2Cl_2 (8 ml). The combined organics were dried (Na_2SO_4), filtered, evaporated *in vacuo* and the residue column chromatographed (1 : 9 EtOAc/petroleum ether) to give rac-**30** as a yellow crystalline solid (1.21 g, 95%). A small portion of the reaction mixture was examined by ^{1}H NMR spectroscopy before chromatography to confirm the absence of the corresponding diastereoisomer.

Similarly prepared was meso-**30**, also as a yellow crystalline solid (96% yield).

*Used as a 1 : 1 mixture of **21** and $TMSCH_2CO_2Et$[14]

(R)-(R*)-1,1'-bis(3-[ethyl 3-phenylpropanoate])ferrocene*, rac-**30**

m.p. 72 - 73.5 °C (EtOAc/petroleum ether) (Found: C, 71.73; H, 6.57. $C_{32}H_{34}FeO_4$ requires C, 71.38; H, 6.36%); ν_{max} (liquid) 1723 cm^{-1} (C=O); δ_H ($CDCl_3$) 1.13 (6 H, t, *J* 7.1, -C*H*$_3$), 2.80 (2 H, dd, *J* 15.0, 10.3, -C*H*HCO$_2$Et), 3.01 (2 H, dd, *J* 15.0, 5.1, -CH*H*CO$_2$Et), 3.85 (2 H, brs, Fc), 3.99 - 4.01 (4 H, m, Fc), 4.02 (4 H, qd, *J* 7.1, 1.9, -OC*H*$_2$CH$_3$), 4.08 (2 H, brs, Fc), 4.10 (2 H, dd, *J* 10, 5.1, -C*H*Ph-), 7.18 - 7.29 (10 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 14.07 (-*C*H$_3$), 41.98 (-*C*HPh-), 42.29 (-*C*H$_2$CO-), 60.30 (-O*C*H$_2$CH$_3$), 67.09 (Fc), 68.09 (Fc), 68.49 (Fc), 68.78 (Fc), 92.79 (Fc - *ipso*), 126.53 (Ph - *para*), 127.68 (Ph), 128.22 (Ph), 143.84 (Ph - *ipso*), 171.83 (*C*=O); *m/z* (EI) 538 (M^+, 100%), 211 (12), 153 (31).

(R)-(S)-1,1'-bis(3-[ethyl 3-phenylpropanoate])ferrocene, meso-**30**

m.p 67-69 °C (EtOAc/petroleum ether) (Found: C, 71.55; H, 6.13. $C_{32}H_{34}FeO_4$ requires C, 71.37; H, 6.38%); ν_{max} (liquid) 1724 cm^{-1} (C=O); δ_H ($CDCl_3$) 1.12 (6 H, t, *J* 7.1, -C*H*$_3$), 2.76 (2 H, dd, *J* 15.1, 10.3, -C*H*HCO$_2$Et), 2.96 (2 H, dd, 15.1, 5.1, -CH*H*CO$_2$Et), 3.91 (2 H, brs, Fc), 3.97 (2 H, brs, Fc), 4.01 (4 H, brs, Fc), 4.02 (4 H, qd, J 7.1, 1.7, -C*H*$_2$CH$_3$), 4.14 (2 H, dd, *J* 10.2, 5.0, -C*H*Ph-), 7.16 - 7.28 (10 H, m, Ph); δ_C {^{1}H} ($CDCl_3$) 14.06 (-*C*H$_3$), 42.07 (-*C*HPh-), 42.26 (-*C*H$_2$CO-), 60.30 (-O*C*H$_2$CH$_3$), 67.31 (Fc), 68.18 (Fc), 68.29 (Fc), 68.71 (Fc), 92.78 (Fc - *ipso*), 126.55 (Ph - *para*), 127.69 (Ph), 128.22 (Ph), 143.83 (Ph - *ipso*), 171.85 (*C*=O); *m/z* (EI) 538 (M^+, 100%), 211(34), 153 (37).

Hydrolyses of 1,1'-bis(3-[ethyl 3-phenylpropanoate])ferrocenes rac- *and* meso-**30**. *Synthesis of (R*)-(R*)- and (R)-(S)-1,1'-bis(3-[3-phenylpropanoic acid])ferrocene* rac- *and* meso-**6**

A yellow solution of rac-**30** (0.490 g, 0.91 mmol) in 1 1 MeOH/H_2O (10 ml) containing NaOH (0.08 g) was heated at reflux overnight. After cooling the resultant yellow solution was acidified with dilute hydrochloric acid giving a yellow suspension. The solvent was reduced to low volume *in vacuo* and the product extracted with CH_2Cl_2 (2 x 50 ml), the combined organics dried (Na_2SO_4), filtered and evaporated. Recrystallistion of the residue from approximately 8 : 1 MeOH/petroleum ether gave rac-**6** as a yellow crystalline solid (0.40 g, 91%).

Similarly prepared was meso-**6**, also as a yellow crystalline solid (70% yield).

(R)-(R*)-1,1'-bis(3-[3-phenylpropanoic acid])ferrocene rac-***6**

m.p. 210 - 211 °C (EtOAc/petroleum ether) (Found: C, 69.52: H, 5.26. $C_{28}H_{26}FeO_4$ requires C, 69.72; H, 5.43%); ν_{max} (nujol) 1729 cm^{-1} (C=O); δ_H (DMSO-d_6) 2.80 (2 H, dd, *J* 15.5, 10.6, -C*H*HCO$_2$H), 3.00 (2 H, dd, *J* 15.5, 4.5, -CH*H*CO$_2$H), 3.88 (2 H, brs, Fc), 3.98 (4 H, brs, Fc), 4.00 (2 H, dd, *J* 10.6, 4.5, -*C*HPh-), 4.19 (2 H, brs, Fc), 7.11 - 7.25 (10 H, m, Ph), 12.09 (2 H, brs, -CO$_2$*H*); δ_C {^{1}H} (DMSO-d_6) 41.56 (-*C*H$_2$CO$_2$H), 41.76 (-*C*HPh-), 67.09 (Fc), 68.29 (Fc), 68.74 (Fc x 2), 93.75 (Fc - *ipso*), 126.58 (Ph - *para*), 127.90 (Ph), 128.50 (Ph), 145.13 (Ph - *para*), 173.28 (-*C*O2H); *m/z* (ES) 481 (M-1, 100%).

*(R)-(S)-1,1'-bis(3-[3-phenylpropanoic acid])ferrocene meso-***6**

m.p. 194 - 196 °C (EtOAc/petroleum ether) (Found: C, 69.43: H, 5.62. $C_{28}H_{26}FeO_4$ requires C, 69.72; H, 5.43%); ν_{max} (nujol) 1696 cm^{-1} (C=O); δ_H (DMSO-d_6) 2.77 (2 H, dd, *J* 15.5, 10.7, -C*H*HCO$_2$H), 2.99 (2 H, dd, *J* 15.5, 4.5, -CH*H*CO$_2$H), 3.93 (2 H, brs, Fc), 3.95 (2 H, brs, Fc), 3.99 (2 H, brs, Fc), 4.04 (2 H, dd, *J* 10, 4, -C*H*Ph-), 4.11 (2 H, brs, Fc), 7.11 - 7.25 (10 H, m, Ph), 12.07 (2H, s, -CO$_2$*H*); δ_C {^{1}H} (DMSO-d_6) 41.56 (-*C*H$_2$CO$_2$H), 41.79 (-*C*HPh-), 67.31 (Fc), 68.33 (Fc), 68.50 (Fc), 68.68 (Fc), 93.78 (Fc - *ipso*), 126.61 (Ph - *para*), 127.93 (Ph), 128.50 (Ph), 145.09 (Ph - *ipso*), 173.28 (-*C*O$_2$H); *m/z* (EI) 482 (M^+, 82%), 227 (55), 153 (100).

Acknowledgements

We gratefully thank the Erasmus scheme for support (NG) and F. C. Brown (Steel Equipment) Ltd. for the generous provision of a studentship (AJL).

References and notes

1. Schlogl, K.; Seiler, H. *Tetrahedron Lett.* **1960**, No. 7, 4-8. Rinehart, K. L.; Bublitz, D. E.; Gustafson, D. H. *J. Am. Chem. Soc.*, **1963**, 85, 970-982.
2. Reetz, M. T.; Sauerwald, M. *J. Organomet. Chem.*, **1987**, 328, 155-160.
3. Richards, C. J.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron Lett.*, **1994**, 35, 4215-4218.
4. Crystal data for **14**. $C_{21}H_{22}FeO$, M = 346.24, monoclinic; P121/n, a = 10.374(6), b = 11.172(3), c = 15.018(4) A, β = 108.88(3)°, Z = 4, Mo-K_α radiation λ = 0.71069 A. 6584 reflections were measured giving 2468 unique data. Final wR_2 and R were 0.0830 and 0.0876 for all data [0.0769 and 0.0380 for 1406 with $I>2\sigma(I)$].
5. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.*, **1986**, 108, 3128-3130.
6. Seebach, D.; Golinski, J. *Helv. Chim. Acta*, **1981**, 64, 1413-1423.
7. Yamakawa, K.; Hisatome, M. *J. Organomet. Chem.*, **1973**, 52, 407-424.
8. Nefedova, M. N.; Mamedyarova, I. A.; Petrovski, P. P.; Sokolov, V. I. *J. Organomet. Chem.*, **1992**, 425, 125-130.
9. Crystal data for meso-**29**. $C_{24}H_{22}FeO_2$, M = 398.27, triclinic; P-1, a = 6.994(2), b = 12.210(3), c = 12.404(4) A, α = 112.633(8)°, β = 93.45(3)°, γ = 104.31(3), Z = 2, Mo-K_α radiation λ = 0.71069 A. 4033 reflections were measured giving 2624 unique data. Final wR_2 and R were 0.1241 and 0.0538 for all data [0.1226 and 0.0490 for 2298 with $I>2\sigma(I)$].
10. Crystal data for meso-**6**. $C_{28}H_{26}FeO_4$, M = 514.38, triclinic; P-1, a = 5.9254(6), b = 11.440(6), c = 18.679(11) A, α = 87.686(13)°, β = 84.941(13)°, γ = 84.49(3), Z = 2, Mo-K_α radiation λ = 0.71069 A. 4033 reflections were measured giving 2624 unique data. Final wR_2 and R were 0.0991 and 0.1605 for all data [0.0745 and 0.0465 for 942 with $I>2\sigma(I)$]. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
11. Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.*, **1972**, 37, 3052-3058.
12. See for example, Nesmeyanov, A. N.; Perevalova, E. G.; Ustynyuk, Y. A. *Doklady Akad. Nauk S.S.S.R.*, **1960**, 133, 1105-1107 (*Chem. Ab.* 1960, **54**, 24616f).
13. Prepared using procedure A as described in: House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.*, **1969**, 34, 2324-2336.
14. Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.*, **1972**, 46, 59-71.
15. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.*, **1976**, 98, 2868-2877.

(*Received in UK* 19 *October* 1995; *accepted* 2 *November* 1995)