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CHIRAL RECOGNITION IN THE REACTION OF THE ENOLATE DERIVED FROM $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2OCH_2Ph]$ WITH *CIS*- AND *TRANS*-2,3-EPOXYBUTANE: THE STEREOSELECTIVE SYNTHESIS OF *CIS* AND *TRANS*-βγ-DISUBSTITUTED-γ-LACTONES

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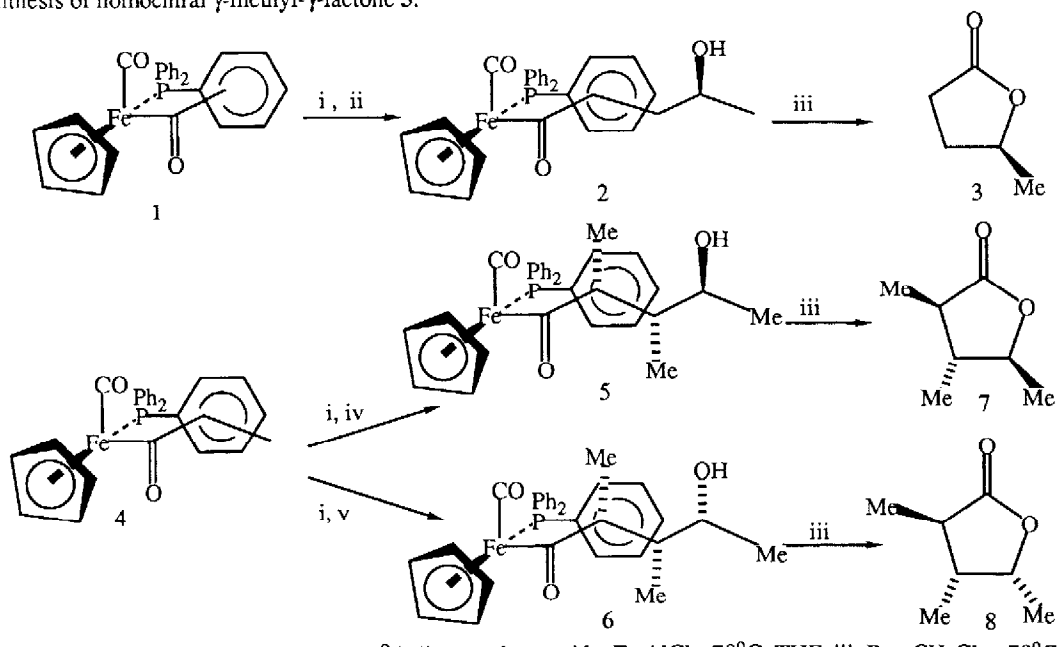
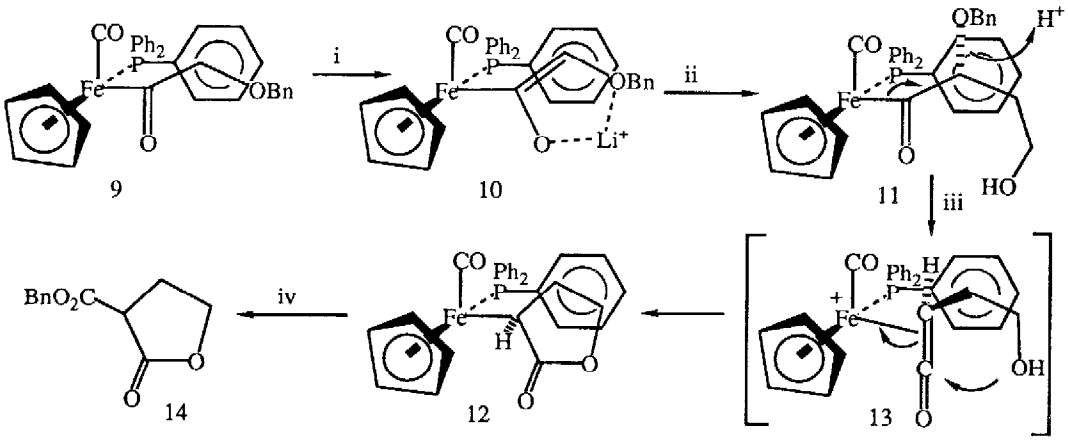
Summary: The reaction between the enolate derived from $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2OCH_2Ph]$ and cis- and trans-2,3-epoxybutane proceeds with a high degree of chiral recognition between the reagents (10:1) to give products which may be converted to β,γ-dimethyl-γ-lactones possessing trans- or cis- stereochemistry.

It has recently been demonstrated that enolates derived from acyl groups attached to the chiral iron auxiliary $[(\eta5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ undergo reactions with epoxides with high degrees of chiral recognition, the products of which may be decomplexed to γ-lactones bearing a variety of substitution patterns. For example, the enolate derived from the acetyl complex **1** reacts with propylene oxide, (in the presence of diethylaluminium chloride catalyst) to give **2** as a single diastereoisomer (>30:1), thereby indicating that each enolate enantiomer reacts exclusively with only one epoxide enantiomer. The relative configuration within the product **2** was established by X-ray crystal structure analysis as RS(SR). Oxidative decomplexation of **2** efficiently produced the γ-methyl-γ-lactone **3**.[1] A similar chiral recognition to the extent of 88:12 occurs in the reaction of the enolate derived from the ethyl acyl complex **4** with either *cis*- or *trans*-2,3-epoxybutane. The major diastereoisomers from each reaction (**5** and **6**, illustrated below) were decomplexed to the α,β,γ-trimethyl-γ-lactones **7** and **8** respectively.[2] The reaction of homochiral iron acetyl complex with racemic propylene oxide resulted in the synthesis of homochiral γ-methyl-γ-lactone **3**.[3]



Reagents i. n-BuLi, THF, -78°C, ii. propylene oxide, Et_2AlCl, -78°C, THF, iii. Br_2, CH_2Cl_2, -78°C, iv. *cis*-2,3-epoxybutane, $BF_3.Et_2O$, -78°C, v. *trans*-2,3-epoxybutane, $BF_3.Et_2O$, -78°C.

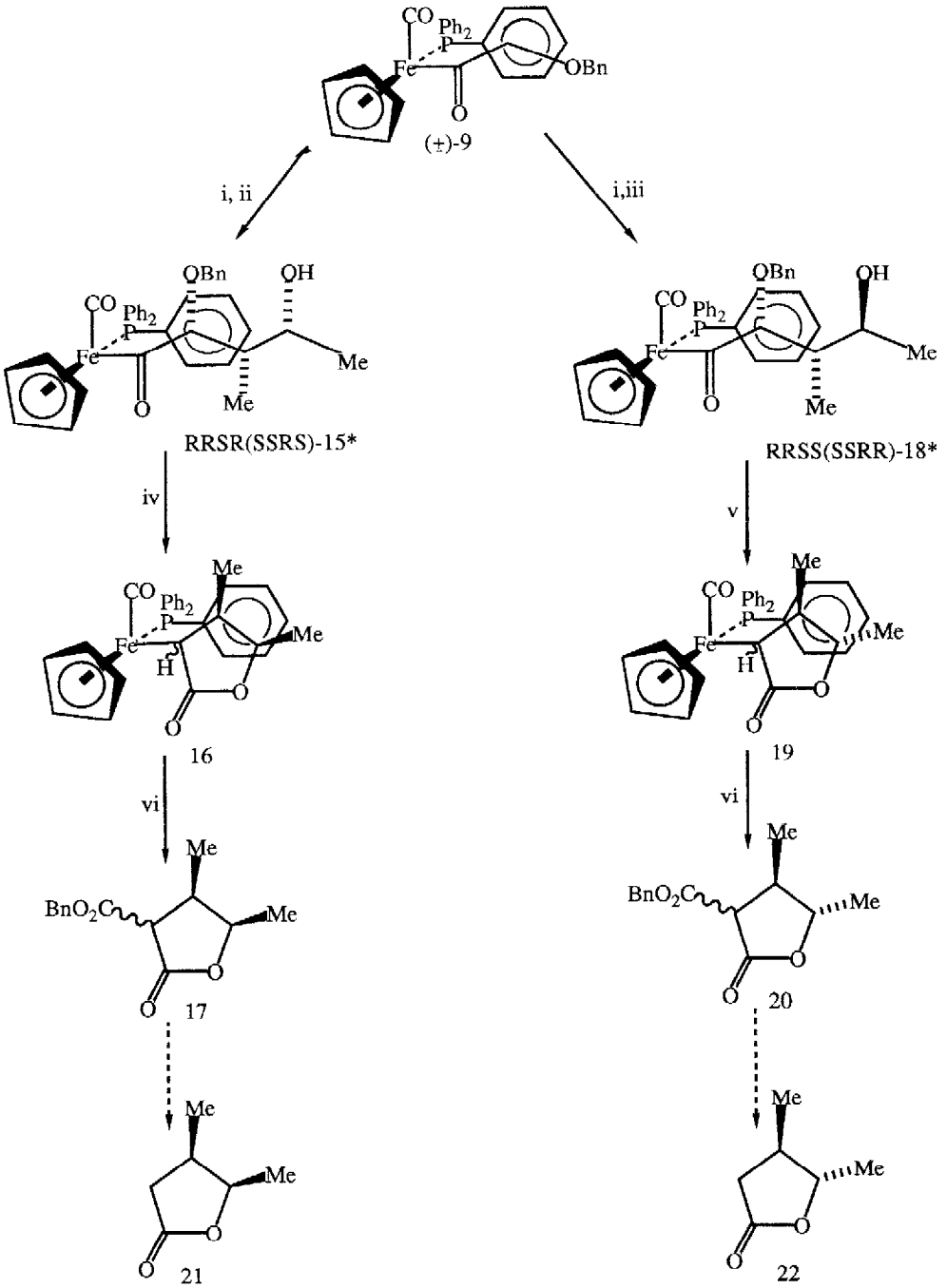
Unfortunately, an attempt to obtain chiral recognition in the reaction of acetyl complex **1** with *cis*- or *trans*-2,3-epoxybutane led to a complex mixture of products in each case, therefore precluding the development of a synthetic route towards homochiral β,γ-disubstituted-γ-lactones.[3] In order to fill this gap in methodology we wished to find a suitably functionalised iron acyl complex containing an α-substituent which could be removed after controlling the addition of a disubstituted epoxide to the derived enolate. In practice, the α-benzyloxy iron acyl complex **9** proved to be such a reagent. Reaction of the enolate **10** derived from **9** with ethylene oxide, (in the presence of diethylaluminium chloride), resulted in the completely stereoselective (>100:1) formation of a single diastereoisomer of product **11**, possessing the relative stereochemistry RR(SS), in 65% yield. This stereochemistry is the result of the addition of the electrophile to the face of the E enolate **10** away from the triphenylphosphine group when it lies in the *anti* (O⁻ to CO) conformation.[4] Treatment of **11** with trifluorosulphonic acid (stoicheiometric) resulted in a quantitative stereospecific rearrangement to the diastereoisomerically pure α-metalla-lactone **12**, *via* a rearrangement process involving an iron-bound ketene intermediate **13**.[5] Oxidative decomplexation of **12** using bromine in the presence of benzyl alcohol, (dichloromethane, -78°C), resulted in the generation of the α-carboxybenzyl lactone **14** in 76% yield.[6]



Reagents i. n-BuLi, -78°C, THF, ii. ethylene oxide, Et_2AlCl, THF, -78°C, iii. TfOH, CH_2Cl_2, 20°C, iv. Br_2, BnOH, -78°C, CH_2Cl_2.

Having clearly demonstrated the applicability of iron complex **9** to the synthesis of γ-lactones, attention was turned to its reactions with 1,2-disubstituted epoxides. Deprotonation of the α-benzyloxy iron acyl complex **9** with n-BuLi followed by treatment with *trans*-2,3-epoxybutane in the presence of boron trifluoride etherate resulted in the formation of the γ-hydroxy product **15** as a mixture of two diastereoisomers in the ratio 10:1 (81% yield), from which the major product was obtained pure by a single recrystallisation from dichloromethane/hexane. An X-ray structure analysis was carried out on the major diastereoisomer of **15** which was found to contain the relative stereochemistry RRSR(SSRS).[7] The relative stereochemistry of the iron to the α-centre was consistent with that assigned to **11** above for the addition of ethylene oxide.

The relative stereochemistry in the major diastereoisomer of **15** indicates that the iron acyl complex of R configuration has reacted selectively with the *trans*- epoxide of RR configuration with concerted S_N2 epoxide ring opening. The 10:1 diastereoisomeric mixture of **15** was prone to decomposition on treatment with trifluorosulphonic acid but could be converted to the corresponding α-metalla lactone **16** without the isolation of the γ-hydroxy complex by the addition of one further equivalent of boron trifluoride etherate, *via* the



Reagents i. n-BuLi, -78°C, THF, ii. (±)-*trans*-2,3-epoxybutane, $BF_3.Et_2O$
iii. *meso-cis*-2,3 epoxybutane, $BF_3.Et_2O$, iv. 1 eq. $BF_3.Et_2O$, THF, 0°C,
v. TfOH, 20°C, CH_2Cl_2, vi. Br_2, BnOH, -78°C, CH_2Cl_2.

*Major diastereoisomer

rearrangement described above (68% overall from **9**). The product consisted of a mixture of three diastereoisomers in the ratio 18:3:2, of which the major diastereoisomer **16** possessed the relative configurations RSSR(SRRS). The two minor products are; i) an α-epimer of the major diastereoisomer of **16** due to epimerisation at this position under conditions of strong acid[8] and ii) a product from the rearrangement of the minor γ-hydroxy diastereoisomer of **15**. The mixture of diastereoisomers **16** was decomplexed under identical conditions to those described above for **11** to give the lactone **17** as a 3:1 mixture of epimers at the α-position (69% yield). The *cis* stereochemistry was confirmed by the characteristic position of the methine OCH protons in the ^{1}H n.m.r. spectrum of the lactones at δ 4.85.[9,10]

Chiral recognition, to the extent of 10:1, was also found to occur in the discrimination between the two terminii of a *meso-cis* epoxide. Reaction of the enolate **10** with *meso-cis*-2,3-epoxybutane gave a mixture of two diastereoisomers **18** in a ratio of 10:1 and in a yield of 90%. By analogy with **14** the major diastereoisomer of **18** was assigned the relative stereochemistry RRSS(SSRR).

Treatment of the major diastereoisomer of **18** (purified by a single recrystallisation from dichloromethane/hexane) with one equivalent of trifluorosulphonic acid at 20°C for two hours in dichloromethane solution gave the α-metalla–γ-lactone **19** (81%) *via* the rearrangement process described previously[5] as an 8:1 mixture of epimers at the α-position due to acid catalysed epimerisation.[8] In this case the major diastereoisomer of **19** was assigned the relative configuration RSSS(SRRR).

Oxidative decomplexation of **19** with bromine in the presence of benzyl alcohol gave the α-carboxybenzyl-*trans*–β,γ-dimethyl–γ-lactone **20** as a 3:1 mixture of epimers at the α-position (76%). The *trans* stereochemistry in the lactone was confirmed by the characteristic positions of the OCH methine resonance in the ^{1}H n.m.r. spectrum at *ca* δ4.09, significantly upfield of the same proton in the *cis* lactone.[9,10] Neither product of the decomplexation reaction contained peaks in the ^{1}H n.m.r. spectrum corresponding to the products **17** of alternative β,γ-relative stereochemistry, obtained from the *trans*-2,3-epoxybutane.

Conversion of **17** and **20** to the lactones **21** and **22** respectively by ester hydrolysis followed by decarboxylation has been reported.[10] Complex **9** may be obtained in optically pure form by hydroxylation (using MoOPH[11] oxidant) of the commercially available methyl acetyl complex **1**.[7] Therefore the utility of complex **9** as a chiral malonate equivalent suitable for the asymmetric synthesis of β,γ-disubstituted–γ-lactones *via* reactions involving chiral recognition has been demonstrated.

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