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Asymmetric Synthesis of 1- and 1,1'-Ferrocenepropanoic Acids

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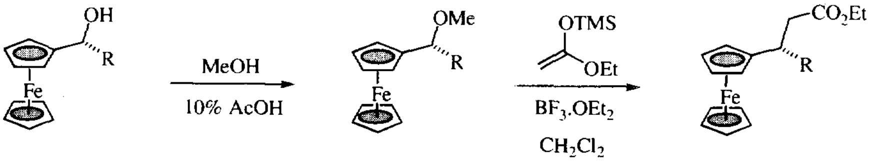
Abstract: α-Ferrocenyl alcohols obtained from oxazaborolidine catalysed reduction of ferrocenyl ketones, were converted to their corresponding ferrocenylmethyl methyl ethers on treatment with MeOH/AcOH. Subsequent $BF_3.OEt_2$ promoted addition of 1-ethoxy-1-(trimethylsilyloxy)ethene followed by ester hydrolysis gave 1- and 1,1'-ferrocenepropanoic acids in high (92 - 96%) enantiomeric excess. Copyright © 1996 Elsevier Science Ltd

We recently reported that addition of silyl enol ethers and silyl ketene acetals to racemic ferrocenylmethyl ethers promoted by $BF_3.OEt_2$ proceeds with clean carbon-carbon bond formation to give ferrocenyl adducts in high yield.[1] Following reports on the highly enantioselective oxazaborolidine reduction of both 1- and 1,1'-ferrocenyl ketones,[2,3] we were prompted to use the products of these reactions as starting materials for the synthesis of enantiomerically enriched ferrocenepropanoic acids. Our preliminary results are reported in this paper.

The previously described CBS-reduction methodology[2] gave α-ferrocenyl alcohols **1a-d** for which we were unable to detect the minor enantiomers when their ^1H NMR spectra were recorded in the presence of excess $Eu(tfc)_3$ in $CDCl_3$.[2] Subsequent treatment with 10% acetic acid in methanol[4] gave ethers **2a-d** in good yield (Scheme 1). The absolute configuration of **2a** was determined by comparison of its rotation $[\alpha]_D^{23}$ = +29.6 (*c* 0.93, EtOH) with that determined previously for (*R*)-**2a**, $[\alpha]_D^{25}$ = +27.5 (*c* 2, EtOH)[5] confirming that methanolysis of **1a** proceeds with overall retention of configuration.



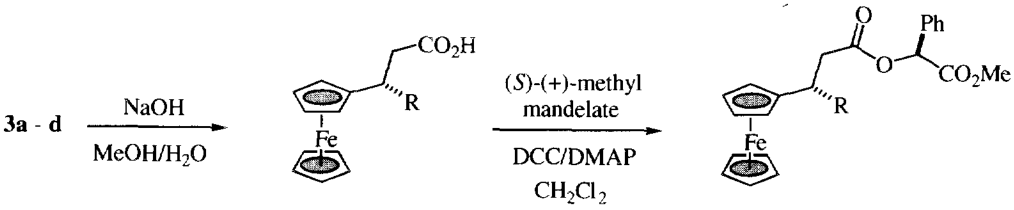
1a R = Me
1b R = Ph
1c R = p-$C_6H_4OCH_2Ph$
1d R = p-C_6H_4Br

2a 98%
2b 92%
2c 70%
2d 95%

3a 95%
3b 97%
3c 46%
3d 76%

Scheme 1

Treatment of **2a-d** with two equivalents of 1-ethoxy-1-(trimethylsilyloxy)ethene and one equivalent of $BF_3.OEt_2$ in CH_2Cl_2 cooled in an acetone/cardice bath, followed by warming of the reaction mixture to room temperature, gave esters **3a-d**. The enantioselectivities of these two step procedures were determined by first hydrolysing the esters to their corresponding acids, followed by DCC mediated coupling with (*S*)-(+)-methyl mandelate (Scheme 2).



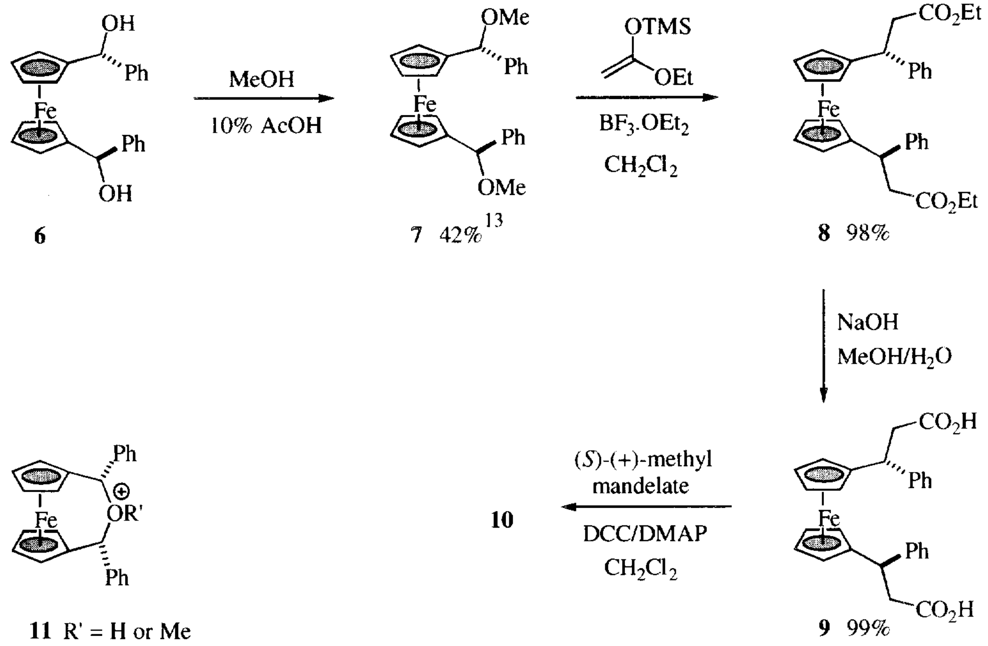
4a 66%
4b 93%
4c 83%
4d 81%

5a - d

Scheme 2

Preliminary coupling of the racemic acids **4a-d** with (*S*)-(+)-methyl mandelate revealed base line separation in the ^1H NMR spectra (400 MHz, $CDCl_3$) for either the methyl and/or methine singlets in the resulting diastereomeric esters. Thus enantiomeric excesses for **4a** (92%)[6], **4b** (96%)[7], **4c** (92%)[8] and **4d** (96%)[9] were readily determined. The absolute configurations depicted in Schemes 2 and 3 are based on the assumption that silyl ketene acetal addition proceeds with overall retention of configuration, due to stereospecific formation and reaction of the intermediate α-ferrocenyl carbenium ions. This is well documented in ferrocene chemistry,[5,10] and also for chromium tricarbonyl stabilised benzylic carbenium ions.[11] The high enantiomeric excesses obtained reflect the configurational stability of the α-ferrocenyl carbenium ions under the reaction conditions.

This methodology was extended to the enantiomerically enriched diol **6** obtained by CBS-reduction of the corresponding 1,1'-dibenzoylferrocene (Scheme 3).[3] Although we had previously shown that methanolysis and silyl ketene acetal addition to a racemic mixture of **6** proceeds with complete retention of relative configuration,[1] we were concerned that these reactions might proceed *via* meso intermediates **11** which would result in a loss of enantioselectivity with a non-racemic substrate. Repetition of the reaction sequence gave **7** and then **8**, as single diastereoisomers. Ester hydrolysis and coupling with excess (*S*)-(+)-methyl mandelate showed the acid **9** to have an enantiomeric excess of 92%[12] revealing selectivity for the 1,1'- derivative to be as high as the monosubstituted examples, and excluding the possibility of intermediates of type **11** in these reactions.



Scheme 3

In summary, this work reports a high yielding and highly enantioselective route to 1- and 1,1'-ferrocenepropanoic acid derivatives. We are currently using these as intermediates in the synthesis of optically active bridging ferrocenophanes on which we aim to report in due course.

Acknowledgements

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References and Notes

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2. Wright, J.; Frambes, L.; Reeves, P. *J. Organomet. Chem.*, 1994, **476**, 215.
3. Schwink, L.; Knochel, P. *Tetrahedron Lett.*, 1996, **37**, 25.
4. Experimental methods for methanolysis, silyl ketene acetal addition and ester hydrolysis are as previously described in reference 1.
5. The previous synthesis of non-racemic **2a** used resolved (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine followed by quaternisation and treatment with wet acetonitrile, Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.*, 1972, **37**, 3052.
6. **5a** 2.77 (1 H, dd, *J* 15.2, 4.6, -C*H*HCO$_2$-), 5.89 (1 H, s, -OC*H*(CO$_2$CH$_3$)Ph). Corresponding peaks for minor diastereoisomer, 2.69 (dd, *J* 15.1, 4.7), 5.87 (s).
7. **5b** 5.76 (1H, s, -OC*H*(CO$_2$CH$_3$)Ph). Corresponding peak for minor diastereoisomer, 5.80 (s).
8. **5c** 3.64 (3 H, s, -CO$_2$C*H*$_3$), 5.76 (1H, s, -OC*H*(CO$_2$CH$_3$)Ph). Corresponding peaks for minor diastereoisomer, 3.56 (s), 5.82 (s).
9. **5d** 3.64 (3 H, s, -CO$_2$C*H*$_3$), 5.77 (1H, s, -OC*H*(CO$_2$CH$_3$)Ph). Corresponding peaks for minor diastereoisomer, 3.57 (s), 5.80 (s).
10. a) Hill, E. A.; Richards, J. H. *J. Am. Chem. Soc.*, 1961, **83**, 4216. b) Ratajczak, A.; Misterkiewicz, B. *J. Organomet. Chem.*, 1975, **91**, 73. c) For an exception due to the influence of other elements of chirality within a molecule see, Malezieux, B.; Gruselle, M.; Troitskaya, L. L.; Sokolov, V. I.; Vaissermann, J. *Organometallics*, 1994, **13**, 2979.
11. Davies, S. G.; Donohoe, T. J. *Synlett*, 1993, 323.
12. **10** 5.74 (1H, s, -OC*H*(CO$_2$CH$_3$)Ph. Corresponding peak for minor diastereoisomer, 5.77 (s).
13. Yield calculated from 1,1'-dibenzoylferrocene. The product **7** was isolated by filtration from 10% AcOH/MeOH on completion of the reaction. The crude diol **6** cannot be purified by SiO$_2$ chromatography as this promotes cyclisation to the meso 7-oxa[3]-ferrocenophane.

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