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STEREOSELECTIVE SYNTHESIS OF *ERYTHRO*-β-HYDROXY CARBOXYLIC ACIDS VIA IRON ACYL COMPLEXES

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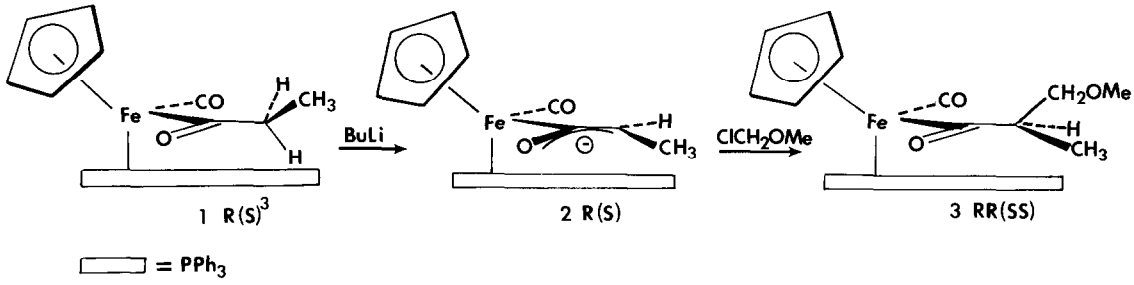
Summary: β-Hydroxy acyl ligands bound to $(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)$ are stereoselectively alkylated on the α-carbon to give after decomplexation *erythro*-β-hydroxy carboxylic acids.

Alkylation of the lithium enolates derived from $(\eta^5\text{-}C_5H_5)Fe(PPh_3)(CO)(COCH_2R)$ results in highly stereoselective carbon-carbon bond formation.[1] The relative configurations of the new chiral centres are those expected from alkylation of the (E)-enolate in the anti (O^- to CO) conformation from the unshielded face.[2] When the group on the new chiral centre is methyl the relative configuration of C_α to Fe can be readily assigned by n.m.r. spectroscopy; the methyl doublet for the RR,SS diastereomers appears between δ 0.0 - 0.5 whereas for the RS,SR diastereomers it appears between δ 0.8 - 1.3. A further example of this stereoselective alkylation is provided by the reaction with $ClCH_2OMe$ of the (E)-enolate 2, derived from the ethyl acyl complex 1, which gave 3 (RR,SS) with greater than 95% stereoselectivity.



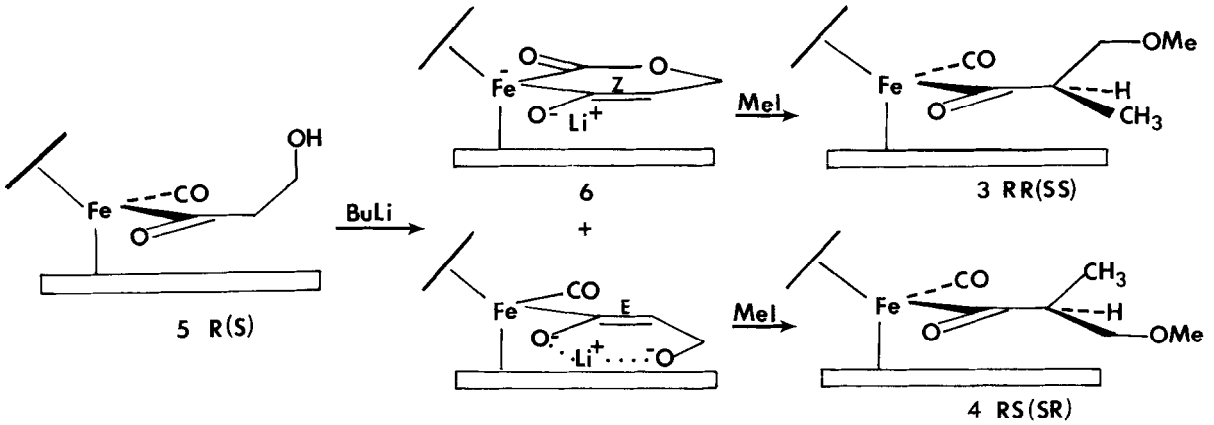
1 R(S)[3] 2 R(S) 3 RR(SS)

□ = PPh_3

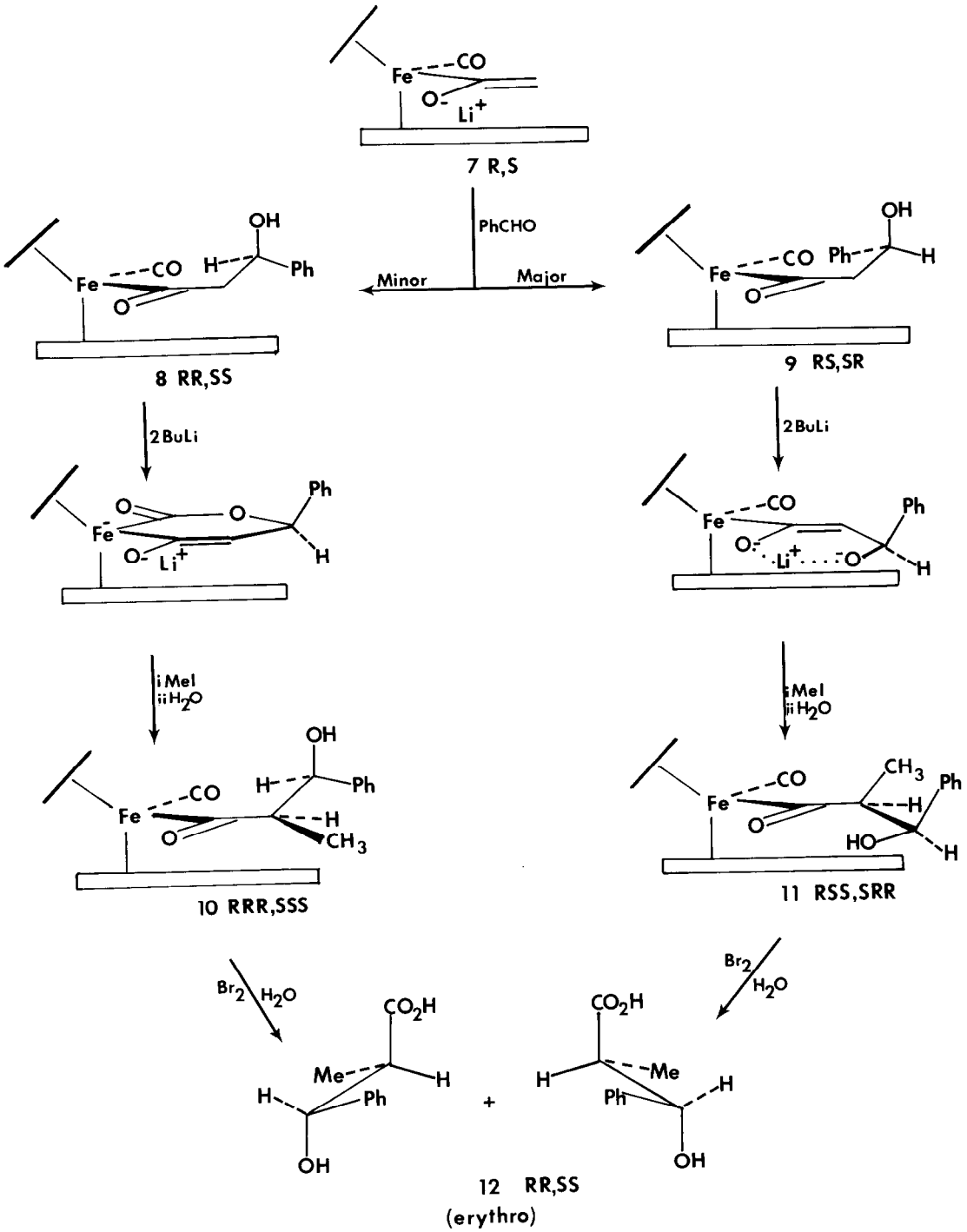
We now report that the β-hydroxy acyl ligands can preferentially form (Z)-enolates on treatment with excess butyl lithium and that this can be exploited for the synthesis of *erythro*-β-hydroxy carboxylic acids.

Treatment of $[(C_5H_5)Fe(CO)_2]^-$ with ethylene oxide generates $(C_5H_5)Fe(CO)_2(CH_2CH_2OH)$ which gives the β-hydroxy acyl complex 5 on treatment with triphenylphosphine in acetonitrile at reflux. Reaction of 5 with two equivalents of n-butyl lithium followed by

excess methyl iodide gives the β-methoxy acyl complexes 3 and 4 in the ratio 3:2. The relative configurations were assigned on the basis of their n.m.r. spectra which contained a doublet for the major diastereomer 3 at δ 0.32 characteristic of the RR,SS diastereomer while the doublet belonging to the minor diastereomer 4 (RS,SR) appeared at δ 1.12. The major diastereomer 3 is that expected from alkylation of the (Z)-enolate 6 from the unhindered face with the minor diastereomer 4 coming from the (E)-enolate. The relative lack of preference for enolate geometry in this case is presumably because of some lactone formation via the carbon monoxide ligand prior to enolate formation leading to the otherwise disfavoured (Z)-enolate. This phenomenon has been observed previously for other types of compound.[4] In confirmation of this stereochemical assignment the major diastereomer was identical to 3 prepared by the alternative method from 2 and $ClCH_2OMe$ described above.



We[5] and others[6] have previously reported that the reaction of the lithium enolate 7 with benzaldehyde produces the β-hydroxy acyl complexes 8 and 9 with little stereoselectivity, but it was not possible to assign their relative stereochemistries. Chromatography/fractional crystallisation allowed the minor 8 and major 9 isomers to be separated. Treatment of the minor isomer 8 with two equivalents of butyl lithium at -78^{o} followed by methyl iodide stereoselectively (> 95%) generated one diastereomer of the α-methyl β-hydroxy acyl complex 10. The relative configurations of the three chiral centres in 10 were established as follows. The n.m.r. spectrum of 10 contained a methyl doublet at δ 0.10 consistent with the relative configuration of Fe to C_{α} being RR,SS. Decomplexation of 10 gave the known *erythro*-β-hydroxy acid 12[7] and hence established the C_{α} to C_{β} relative configurations as RR,SS.


Fe
CO
O
Li+
7 R,S
PhCHO
Minor
Major
OH
H
Ph
8 RR,SS
9 RS,SR
2BuLi
O
Li+
10 RRR,SSS
11 RSS,SRR
iMeI
iiH2O
CH3
HO
Br2
H2O
CO2H
Me
12 RR,SS
(erythro)

Therefore the $FeC_{\alpha}C_{\beta}$ relative configurations in 10 are RRR,SSS. These results also allow assignment of the relative configurations of Fe to C_{β} in the minor diastereomer 8 as RR,SS.

Similar methylation of the major diastereomer 9 selectively gave 11 which on decomplexation also gave the *erythro*-β-hydroxy acid 12. The n.m.r. spectrum of 11 showed a methyl doublet at δ 0.87. Hence the relative configurations of $FeC_{\alpha}C_{\beta}$ for 11 are RSS,SRR and those of FeC_{β} for 9 are RS,SR.

Both diastereomers 8 and 9 gave after methylation and decomplexation the *erythro*-β-hydroxy acid 12. This is consistent with the dianion from 8 being the cyclised lactone i.e. the (Z)-enolate with the β-phenyl away from the PPh_3. A similar cyclised lactone from the dianion of 9 would place the β-phenyl towards the PPh_3 and it would therefore prefer to exist as the (E)-enolate as shown.

The above procedures allow the synthesis of *erythro*-β-hydroxy acids with high diastereoselective control. Their extension to asymmetric synthesis requires development of efficient resolution procedures for the initial iron complexes and methods for achieving high stereoselectivities in the initial reaction of 7 with aldehydes. These will be reported in the near future along with other examples of self-compensating stereochemical control.

References

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3. All compounds in this paper are racemic. The order of priority for assignment of configuration at iron is $C_5H_5 > PPh_3 > CO > COR$. For consistency only those with R configuration at iron are shown.
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