Tetrahedron Vol. 49, No. 25, pp. 5635-5647, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

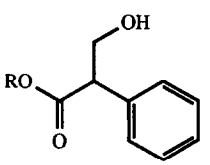
Asymmetric Synthesis of (*S*)-(-)-Methyl Tropinate: Application of the Iron Acyl Complex (*S*)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2Ph$] as a Homochiral Phenylacetate Enolate Equivalent.

Teresa M. Baker, Graham J. Bodwell, Stephen G. Davies*, Alison J. Edwards and Michael R. Metzler
The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, U.K.

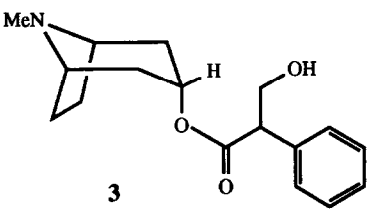
(*Received in USA* 19 *January* 1993; *accepted* 29 *March* 1993)

Summary: Treatment of the lithium enolate derived from homochiral (*S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$ **5** with benzyne afforded the homochiral phenylacetyl complex (*S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2Ph$] **4**. Treatment of the lithium enolate derived from **4** with $ClCH_2OCH_2Ph$ furnished the homochiral α-substituted complex (*S*,*S*)-(-)-[(η^5-C_5H_5)-Fe(CO)(PPh_3)$COCH(CH_2OCH_2Ph)Ph$] **14** (d.e. > 98%), which on decomplexation and debenzylation afforded (*S*)-(-)-methyl tropinate (*S*)-**2** (e.e. > 98%).

Introduction: α-Substituted phenylacetate derivatives have widespread medicinal importance;[1] many α-arylalkanoic acids have potent anti-inflammatory and analgesic properties, and consequently many syntheses of these compounds have appeared in the literature.[2] Perhaps the most widely known is tropic acid **1**, the biologically active acid moiety of atropine **3**, which is a parasympatholytic alkaloid isolated from *Atropa belladonna* L., *Datura stramonium* L., and other Solanaceae.[3] (*S*)-(-)-Hyoscyamine (*S*)-**3**, the naturally occurring enantiomer, has previously been obtained by resolution of atropine or from reaction of (-)-acetyltropyl chloride (obtained by classical resolution of tropic acid[4]) and tropine hydrochloride.[3] To date we are not aware of an asymmetric synthesis of tropic acid in the literature, the major difficulty being the propensity for the acid moiety to undergo racemisation.



1 R = H **2** R = Me

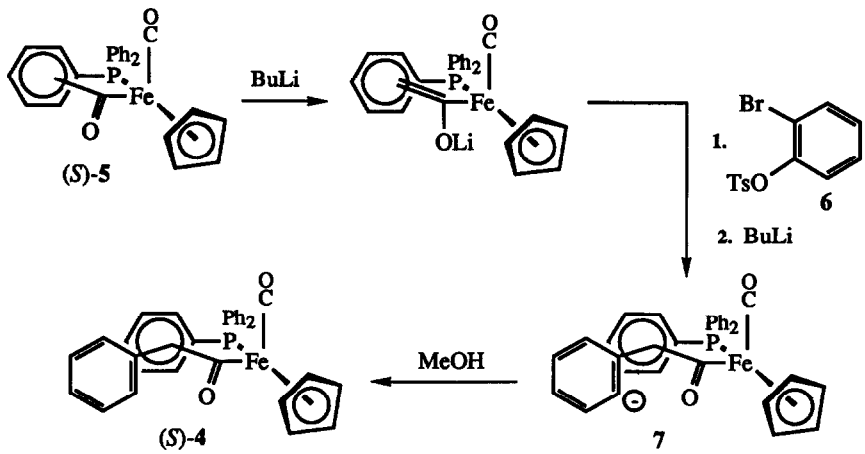


3

We have previously demonstrated[5] that the iron chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] exerts powerful stereochemical control in a wide variety of reactions of attached acyl ligands. In particular, enolates derived from iron acyl ligands undergo highly stereoselective alkylation reactions[6] and therefore we envisaged that incorporation of a phenylacetyl moiety on the auxiliary would be a useful precursor in the synthesis of homochiral phenylacetate derivatives. We report herein the synthesis of a homochiral phenylacetate equivalent [(η^5-C_5H_5)Fe(CO)(PPh_3) $COCH_2Ph$] **4** and its application in the asymmetric synthesis of (*S*)-(-)-methyl tropinate (*S*)-**2**. A mechanism for decomplexation of the iron auxiliary is proposed. Guo and Zamojski have reported recently poor stereoselectivities in the alkylations of racemic (*RS*)-**4** and these results are discussed.[7]

Results and discussion: The reaction of enolates with benzyne is well known,[8] but many attempts to generate α-arylketones using this method have resulted in only low yields of the desired product, perhaps

because the base used to generate benzyne can in some cases also act as a nucleophilic trap for the benzyne. However, side reactions may be minimised by use of lower temperatures and slow addition of the base used to generate the benzyne. Thus, treatment of the racemic enolate derived from (*RS*)-**5** with the bromotosylate **6**,[9] followed by addition of butyllithium at -100°C to generate benzyne, furnished, after protic work-up, the desired racemic iron phenylacetyl complex (*RS*)-**4** in 84% yield. The structure of complex (*RS*)-**4** was confirmed by X-ray crystallographic analysis. Similar treatment of homochiral (*S*)-(+)-**5** generated the homochiral complex (*S*)-(+)-**4** $[\alpha]_D^{21} = +124.8$ (c 0.23, toluene) (Scheme 1).



Scheme 1

The X-ray crystal structure of racemic (*RS*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2Ph$] (*RS*)-**4** is shown in Figure 1. Selected torsional angles and bond angles are given in Table 1 and the fractional atomic co-ordinates are listed in Table 2.

Table 1. Selected Torsional Angles and Bond Angles for (*RS*)-**4**.

Selected Torsional Angles (°)		Selected Bond Angles (°)	
P-Fe-C1-O1	54	P-Fe-C9	94.8(3)
Fe-C1-C2-C3	166	C1-Fe-C9	95.5(4)
C1-C2-C3-C4	104	P-Fe-C1	89.9(3)

If the above arylation reaction was carried out at -78°C, the anion **7** formed from reaction of the enolate of **5** with benzyne reacted with **6** to give mixtures of **4** and the *ortho*-bromo derivative **8**. Furthermore, reaction of the enolate derived from (*RS*)-**5** with the bromotosylate **6** and only a small amount (0.1 eq) of butyllithium (to generate "catalytic" benzyne) furnished complex (*RS*)-**8** exclusively in 92% yield (Scheme 2).

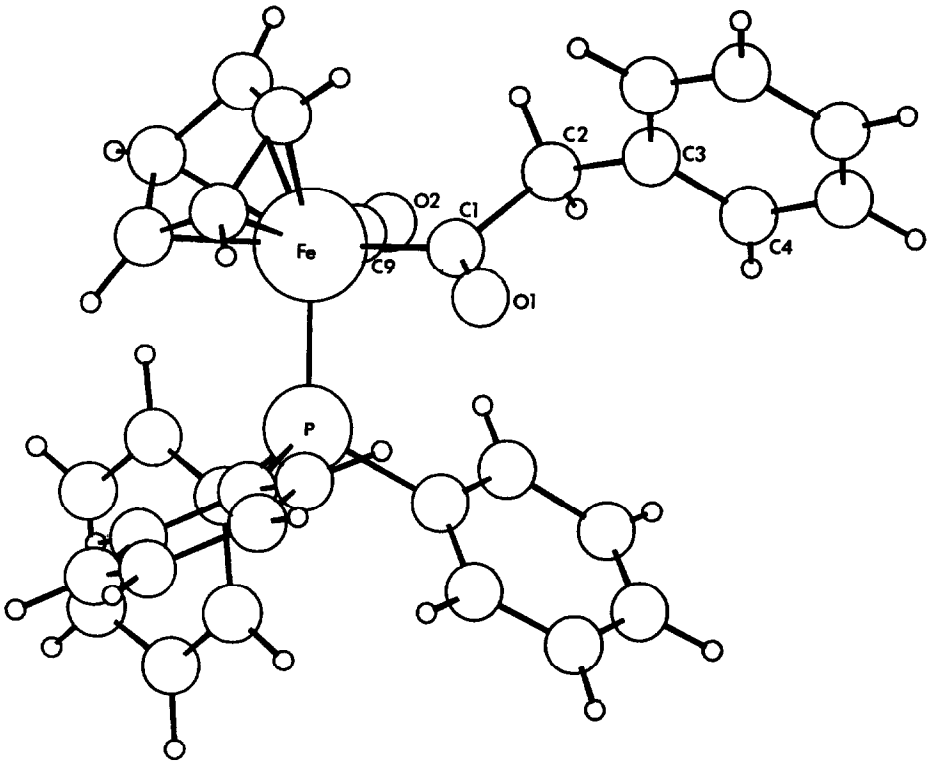
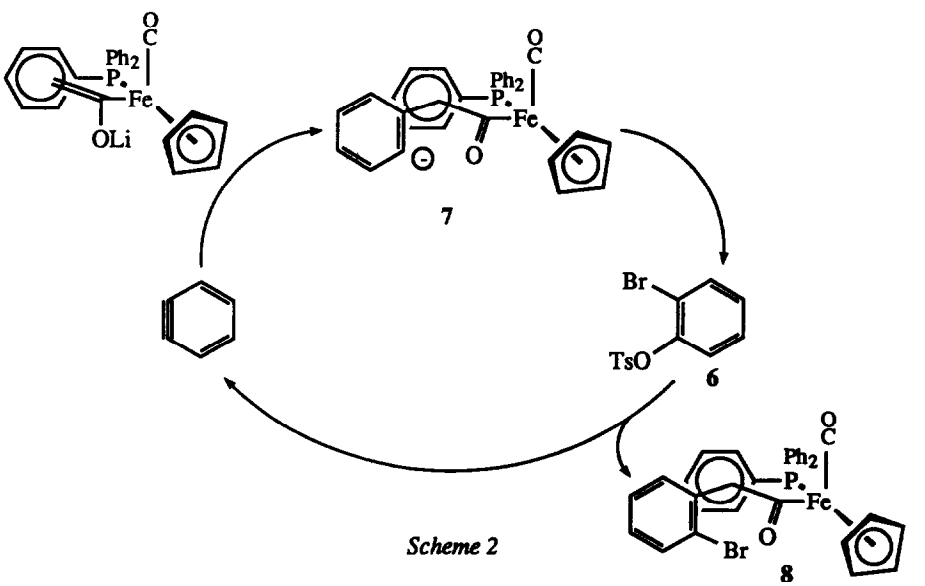


Figure 1. X-Ray crystal structure of (*RS*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2Ph$] (*RS*)-**4**

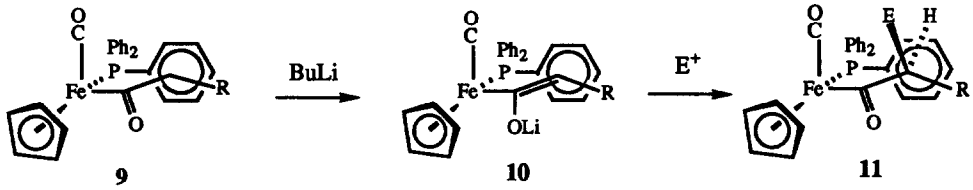


Scheme 2

Table 2. Fractional Atomic Coordinates for (*RS*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2Ph$] (*RS*)-4.

Atom	*x/a*	*y/b*	*z/c*	U_{eq}
Fe(1)	0.2085(2)	0.15996(5)	0.4152(1)	0.0465
P(1)	0.4619(2)	0.15423(8)	0.4788(2)	0.0481
O(1)	0.2739(8)	0.0734(2)	0.5520(7)	0.0654
O(2)	0.2208(8)	0.2396(2)	0.5846(8)	0.0748
C(1)	0.217(1)	0.1122(3)	0.5435(9)	0.0497
C(2)	0.130(1)	0.1216(3)	0.640(1)	0.0607
C(3)	0.110(1)	0.0789(3)	0.7107(9)	0.0549
C(4)	0.206(1)	0.0724(3)	0.847(1)	0.0785
C(5)	0.183(1)	0.0336(4)	0.9156(9)	0.0817
C(6)	0.075(2)	0.0014(3)	0.850(1)	0.0804
C(7)	-0.022(1)	0.0072(3)	0.711(1)	0.0833
C(8)	-0.003(1)	0.0452(3)	0.6436(9)	0.0736
C(9)	0.219(1)	0.2060(4)	0.517(1)	0.0567
C(10)	0.009(1)	0.1219(4)	0.289(1)	0.0619
C(11)	-0.026(1)	0.1711(4)	0.281(1)	0.0704
C(12)	0.073(1)	0.1945(4)	0.231(1)	0.0720
C(13)	0.169(1)	0.1601(4)	0.2100(9)	0.0665
C(14)	0.131(1)	0.1164(4)	0.246(1)	0.0613
C(15)	0.562(1)	0.2071(3)	0.4604(9)	0.0544
C(16)	0.483(1)	0.2460(3)	0.3923(9)	0.0589
C(17)	0.564(1)	0.2859(4)	0.377(1)	0.0668
C(18)	0.727(1)	0.2858(4)	0.434(1)	0.0661
C(19)	0.805(1)	0.2476(4)	0.507(1)	0.0672
C(20)	0.727(1)	0.2086(3)	0.520(1)	0.0607
C(21)	0.520(1)	0.1100(3)	0.3839(9)	0.0554
C(22)	0.572(1)	0.1239(4)	0.286(1)	0.0748
C(23)	0.605(1)	0.0901(5)	0.211(1)	0.0826
C(24)	0.586(1)	0.0449(5)	0.225(1)	0.0857
C(25)	0.535(1)	0.0302(4)	0.325(1)	0.0790
C(26)	0.498(1)	0.0628(3)	0.398(1)	0.0641
C(27)	0.579(1)	0.1394(3)	0.6546(9)	0.0512
C(28)	0.554(1)	0.1661(3)	0.751(1)	0.0675
C(29)	0.654(1)	0.1592(4)	0.890(1)	0.0729
C(30)	0.758(1)	0.1242(5)	0.926(1)	0.0798
C(31)	0.783(1)	0.0987(5)	0.831(1)	0.0886
C(32)	0.695(1)	0.1066(4)	0.697(1)	0.0753

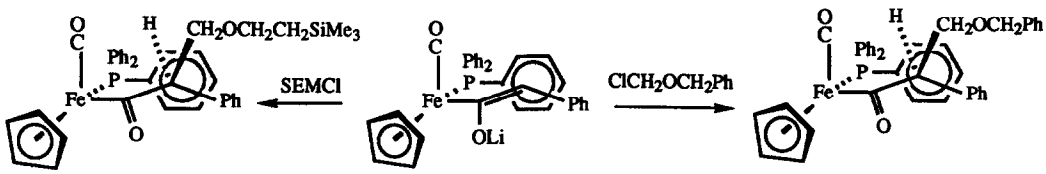
We have previously reported[4,5,10] that deprotonation of the iron acyl complexes **9** with butyllithium gives the corresponding *E*-enolates (Fe *trans* to R) **10**, which react with electrophiles with essentially complete stereoselectivity from the unhindered face in the conformation with the enolate oxygen *anti* to the carbon monoxide ligand, generating diastereoisomers **11** (Scheme 3).



9 **10** **11**

Scheme 3

By analogy with this result, we assumed that the *E*-enolate **12** would be formed upon deprotonation of **4**, and hence the synthesis of (*S*)-methyl tropinate (*S*)-**2** would require the stereoselective introduction of a hydroxymethyl group into the benzylic position of (*S*)-**4**. Reactions of enolates with formaldehyde have been reported to proceed in variable yield, but we didn't anticipate high selectivity with such a reactive electrophile. Recently, Crich[11] reported that 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) was an effective formaldehyde equivalent useful in reactions with ketone enolates, and that several reagents could then be used to cleave the O-$CH_2CH_2SiMe_3$ bond. Thus, reaction of the enolate (*RS*)-**12** derived from (*RS*)-**4** and butyllithium, with SEMCl at -78°C for 6 hrs afforded the complex (*RS,RS*)-**13** as a single diastereoisomer (d.e. > 98%) in 82% yield. However, all attempts to liberate the latent hydroxyl group failed, with forcing conditions resulting in decomposition of the iron complex. It might have been possible to remove the protecting group after decomplexation of the iron, but this was thought unlikely given the necessity of using mild conditions to prevent racemisation. We therefore turned to the benzyl protecting group, which could be removed by catalytic hydrogenation at a later stage. The reaction of the enolate **12** with benzyloxymethyl chloride[12] at -78°C for 6 hrs furnished the complex (*RS,RS*)-**14** as a single diastereoisomer (d.e. > 98%) in 78% yield (Scheme 4). The relative configurations within **13** and **14** were assigned by analogy with all other stereoselective reactions of enolates attached to the iron chiral auxiliary.[5]

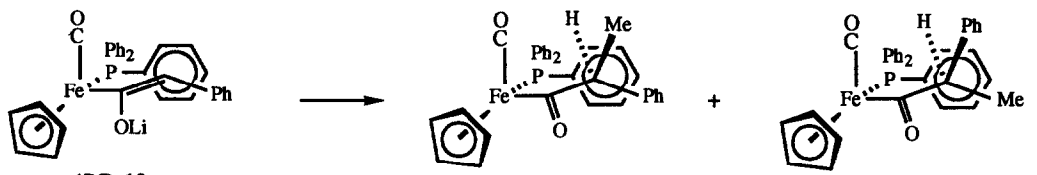


(*RS,RS*)-**13** (*RS*)-**12** (*RS,RS*)-**14**

Scheme 4

In contrast to the completely stereoselective reactions described above, Guo and Zamojski have reported poor selectivities in simple alkylations of the enolate derived from (*RS*)-**4**.[7] Their results apparently require both the formation of the *E*-enolate **12** and its subsequent alkylation from the unhindered face not to be completely stereoselective. These conclusions are incompatible with our observations above and elsewhere.[5]

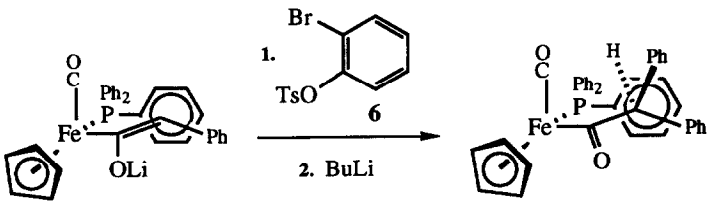
We have also examined the methylation of the enolate **12** derived from **4** and have indeed also found that the selectivity was lower than expected and variable. At best, methylation of (*RS*)-**12** with methyl iodide afforded the α-methyl derivative **15** in 86% yield with a diastereomeric excess of 87% as determined by analysis of the 500 MHz ^{1}H nmr spectrum (Scheme 5). The major diastereoisomer was the expected (*RS,SR*)-**15** as evidenced by the methyl doublet chemical shift at δ 1.34 compared to that for the minor diastereoisomer at δ 0.62.[13] The cyclopentadienyl ^{1}H chemical shifts were also very characteristic δ 4.50 (major) and δ 4.07 (minor) the latter being shielded by the proximity of the phenyl group of the acyl ligand. Our preliminary investigations into the origins of this lack of stereoselectivity have indicated that (*RS,SR*)-**15** is epimerised by strong base and that (*RS,SR*)-**15** slowly decomposes in preference to its epimer (*RS,RS*)-**15** in protic solvents such as methanol, which is used in the quench before work-up. The latter was demonstrated when a solution of the diastereoisomers (*RS,SR*) and (*RS,RS*)-**15** (5:1) in THF/MeOH was treated with NaOMe (catalytic) exposed to air at room temperature for 123 hrs which afforded upon workup a mixture of (*RS,SR*) and (*RS,RS*)-**15** (1:6, which corresponds to diastereoisomeric excess of 71%) in 7% yield. When this reaction was attempted with vigorous exclusion of air only minimal decomposition of both diastereoisomers was observed. These factors combine to lower the overall selectivity and yield, both of which become worse the longer the reaction is left before quench and subsequently also before work-up. The selectivity in the formation of **13** and **14** is presumably not affected by these processes since formation of the enolates derived from them would result in elimination of the β-alkoxy substituent not in epimerisation.[14]



(*RS*)-**12** → (*RS,SR*)-**15** major + (*RS,RS*)-**15** minor

Scheme 5

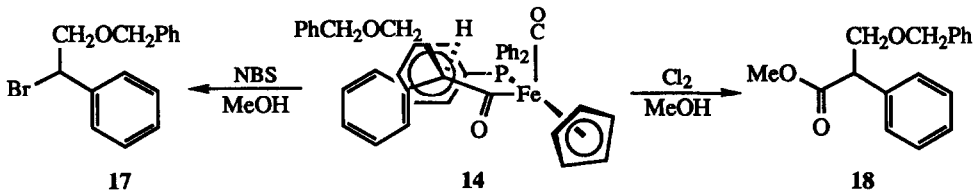
In order to probe the stability of the phenylacetyl complex (*RS*)-**4** the diphenylacetyl derivative (*RS*)-**16** was synthesised in 59% yield by reaction of the enolate (*RS*)-**12** with benzyne (Scheme 6). This sensitive iron complex showed the benzylic hydrogen resonance at δ 5.89 in the ^{1}H nmr spectrum and analysed correctly for $C_{38}H_{31}FeO_2P$. The diphenylacetyl complex (*RS*)-**16** proved to be very unstable in solution decomposing rapidly to a number of side products including $[(\eta^5\text{-}(C_5H_5)Fe(CO)_2(PPh_3)]^+$ which was identified by its characteristic infrared spectrum with Fe-CO absorptions at 2052 and 2008 cm^{-1}.



(*RS*)-**12** → (*RS*)-**16**

Scheme 6

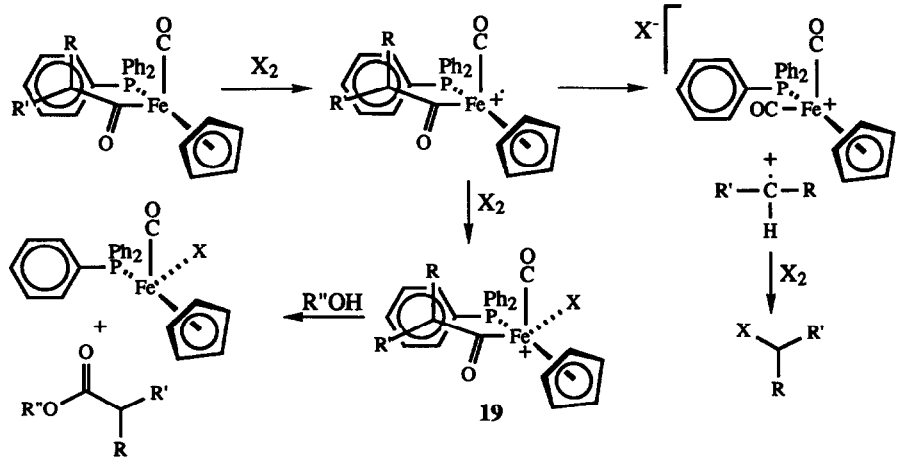
Decomplexation of the iron complex **14** was carried out under mild conditions with *N*-bromosuccinimide in methanolic tetrahydrofuran at -78°C. Reaction occurred on warming the reaction mixture to 0°C, whereupon a green solution was obtained. Work-up and chromatography gave a colourless oil which, from analysis of spectroscopic data, was assigned structure **17** (Scheme 7). This result is in agreement with the observation by Guo and Zamojski[7] that a number of other phenylacetyl iron complexes underwent decarbonylation upon exposure to N-bromosuccinimide. Liebeskind has also reported[15] that some iron acyl species give decarbonylated products under some oxidative decomplexation conditions, and that the degree of decarbonylation is largely dependent on the structure of the complex and on the nature of the oxidant used; bromine being superior to iodine in β-lactam synthesis. When **14** was treated at -78°C with bromine as the oxidant, a 1:1 mixture of the bromide **17** and the required ester **18** was obtained. We have found however that the use of the more powerful oxidant chlorine in the presence of methanol at -78°C gave only a trace of decarbonylated product **17**, with the desired ester **18** as the major product. Furthermore, when the reaction was carried out at -100°C, no decarbonylated product **17** was detected.



17 **14** **18**

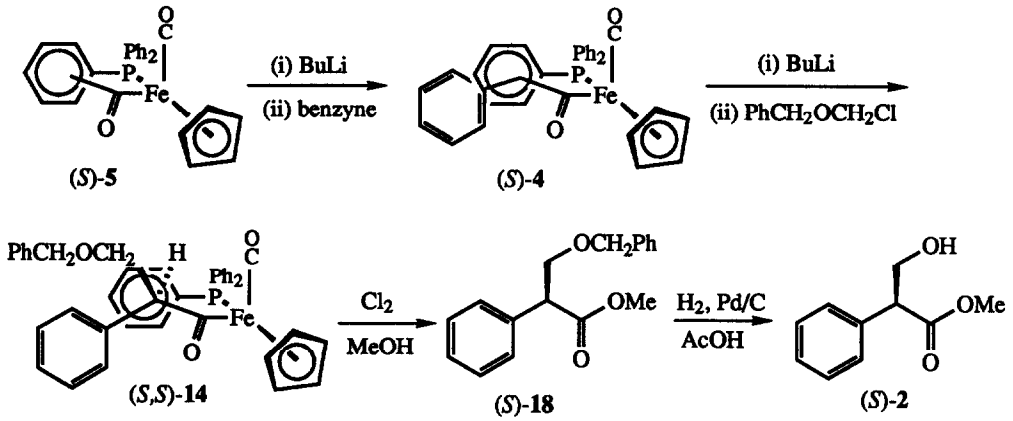
Scheme 7

The mechanism of decomplexation is not well understood. Liebeskind[15] suggested that decomplexation may proceed through the acylium ion **19**. Based on the evidence obtained from the decomplexation of **15**, we propose the following mechanisms are operating (Scheme 8).



Scheme 8

Starting from homochiral (*S*)-(-)-**5** the asymmetric synthesis of (*S*)-(-)-methyl tropinate (*S*)-**2** was achieved by the sequence shown in Scheme 9. The O-protected methyl ester **18** was finally debenzylated by catalytic hydrogenation to furnish (*S*)-(-)-methyl tropinate **2** in 94% yield; $[\alpha]_D^{23}$ = -69.8 (c = 0.875, Me_2CO) {lit.[16] -69.9 (c = 4.947, Me_2CO)}. The overall yield of (*S*)-**2** from (*S*)-**5** was 44%. Correlation of the known[16] absolute configuration of (*S*)-(-)-**2** with (*S,S*)-**14** confirms the configurational assignment of the latter.



Scheme 9

Acknowledgements: We thank BP International Ltd. for a Venture Research Award and the SERC for support

Experimental: All reactions and purifications were performed under nitrogen using standard vacuum line and Schlenk techniques.[17] Removal of all solvents was carried out under reduced pressure. THF was dried over sodium benzophenone ketyl and distilled. Dichloromethane was distilled from calcium hydride. Infra-red spectra were recorded on a Perkin Elmer 1750 Infra-red Fourier Transform Spectrometer. Proton n.m.r spectra and Carbon-13 spectra were recorded on a Bruker AM 500 spectrometer fitted with an Aspect 3000 computer at 500.13 MHz and 125.76 MHz respectively, using $CDCl_3$ as solvent with residual $CHCl_3$ as internal standard and chemical shifts being reported as δ ppm from $(CH_3)_4Si$. Phosphorus-31 spectra were recorded at 101.26 MHz on a Bruker AM 250 spectrometer fitted with an Aspect 3000 computer and are reported as δ ppm from an external reference of trimethylphosphate in D_2O. Electron impact and chemical ionisation (NH_3) mass spectra were recorded on V.G. micromass ZAB 2F instrument using fast atom bombardment (FAB) techniques. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Dyson Perrins Analytical Services (Oxford, U.K.). Homochiral (*S*)-(+)-[$(C_5H_5)Fe(CO)(PPh_3)COCH_3$] was supplied by Oxford Asymmetry Ltd.[18]

(S)-(+)-[$(C_5H_5)Fe(CO)(PPh_3)COCH_2Ph$] **4**. Butyllithium (1.2 eq) was added dropwise to an orange solution of the acetyl complex (*S*)-(+)-**5** (5.0 g, 11 mmol) in THF (100 ml) at -78°C and the resulting dark red solution was stirred at -78°C for 1 hr. The solution was then cooled to -100°C and a precooled (-100°C) solution of the bromotosylate **6** (3.6 g, 11 mmol) was added *via* cannula, followed immediately by the dropwise addition of BuLi (1 eq), such that the temperature of the reaction mixture did not exceed -95°C. The solution was allowed

to warm to -78°C and stirred at this temperature for 1 hr. The reaction was quenched with methanol (5 ml) and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and the reaction mixture was filtered through alumina (Grade V). The solvent was removed from the filtrate *in vacuo* and the crude product was purified by flash chromatography with 50% ether/hexane as eluant. Crystallisation from CH_2Cl_2/heptane furnished (*S*)-**4** (4.9 g, 84%) as orange prisms; $[\alpha]_D^{21}$ = +124.8 (c 0.23, toluene); Found: C, 72.77; H, 5.26. $C_{32}H_{27}FeO_2P$ requires: C, 72.47; H, 5.13%; ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 3.68, 4.21 (each 1H, d, *J* 14.3 Hz, CH_2), 4.34 (5H, d, *J* 1.2 Hz, C_5H_5), 6.87 - 7.54 (20 H, m, ArH); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 71.82 (t, CH_2), 85.18 (d, C_5H_5), 125.63 (d, Ar $C_{para\ to\ C}$), 127.88 (d, Ar $C_{meta\ to\ C}$), 128.08 (dd, $^3J_{PC}$ 8.8 Hz, Ar $C_{meta\ to\ P}$), 129.56 (d, Ar $C_{ortho\ to\ C}$), 129.74 (d, Ar $C_{para\ to\ P}$), 133.43 (dd, $^2J_{PC}$ 9.1 Hz, Ar $C_{ortho\ to\ P}$), 136.51 (s, Ar $C_{ipso\ to\ C}$), 136.53 (d, $^1J_{PC}$ 42.7 Hz, Ar $C_{ipso\ to\ P}$), 220.78 (d, $^2J_{PC}$ 30.2 Hz, C=O), 272.69 (d, $^2J_{PC}$ 20.1 Hz, C≡O); ^{31}P n.m.r. (101 MHz, $CDCl_3$) δ 72.09; *m/z* 531(*M*$^+$+H, 8), 439 (*M*-CH_2Ph, 43), 383(439-2CO, 100), 263(32), 183(20); ν_{max} (cm^{-1}) 1907 (Fe-CO), 1612 (C=O), 1483, 1433, 1093, 979, 752, 696.

A similar reaction with racemic (*RS*)-**5** gave racemic (*RS*)-**4** in 81%. Crystal Data: $C_{32}H_{27}Fe_1O_2P_1$, M_r 530.4, monoclinic, space group $P2_1/n$ (No.14), a = 9.365(1), b = 28.467(2) c = 10.893(1)Å, β = 113.98(1)°, Z = 4, μ (CuKα) = 53.51 cm^{-1}, CAD4 Diffractometer, graphite monochromated CuKα radiation, ρ = 1.328 gcm^{-3}, 4492 reflections ($0 < 2\theta \leq 110°$) measured, 3325 unique, of which 1721 observed $I \geq 3\sigma I$. Data were corrected for Lorentz, polarization[19] and absorption[20]. The structure was solved by Patterson methods[21]. A full matrix least-squares refinement procedure[19] which included positional and anisotropic thermal parameters for all non-hydrogen atoms was used. Hydrogen atoms were included in the model at calculated positions with isotropic thermal parameters included in the refinement. Final R = 0.084, R_w = 0.077 for 352 refined parameters. Determination of this crystal structure was hampered by the extremely weakly scattering nature of the material crystallized. A number of crystals from each of a number of batches were examined before the specimen used (a red prism 0.4 x 0.5 x 1.0 mm) was located. All faces and edges were sharply defined and the specimen showed remarkable clarity yet the intensity of the diffracted X-rays was very weak.

(RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2$(o-BrPh)] **8**. Butyllithium (1.2 eq) was added dropwise to an orange solution of the acetyl complex (*RS*)-**5** (2.0 g, 4.4 mmol) in THF (40 ml) at -78°C and the resulting dark red solution was stirred at -78°C for 1 hr. A precooled (-78°C) solution of the bromotosylate **6** (1.4 g, 4.4 mmol) in THF (15 ml) was added *via* cannula, and the solution was stirred at -78°C for 1 hr. The reaction was quenched with methanol (5 ml) and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and the reaction mixture was filtered through alumina (Grade V). The solvent was removed from the filtrate *in vacuo* and the crude product was purified by flash chromatography with 50% ether/hexane as eluant. Crystallisation from CH_2Cl_2/heptane yielded (*RS*)-**8** (2.5 g, 92%) as orange prisms; Found: C, 62.78; H, 4.13. $C_{32}H_{26}FeBrO_2P$ requires: C, 63.08; H, 4.30%; ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 3.74, 4.68 (each 1H, d, *J* 16.7 Hz, CH_2), 4.55 (5H, d, *J* 1.2 Hz, C_5H_5), 6.23 (1H, dd, *J* 7.3, 0.8 Hz, Ar$H_{ortho\ to\ C}$), 6.95, 7.04 (each 1H, td, *J* 7.3, 0.8 Hz, Ar$H_{para\ to\ Br}$, Ar$H_{para\ to\ C}$), 7.35-7.45 (10H, m, Ar$H_{meta\ to\ P}$, Ar$H_{para\ to\ P}$, Ar$H_{ortho\ to\ Br}$), 7.51 - 7.59 (6H, m, Ar$H_{ortho\ to\ P}$); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 71.40 (t, CH_2), 85.37 (d, C_5H_5), 124.48 (d, Ar $C_{ipso\ to\ Br}$), 126.65, 127.28 (d, Ar $C_{para\ to\ Br}$, Ar $C_{para\ to\ C}$), 128.09 (dd, $^3J_{PC}$ 9.1 Hz, Ar $C_{meta\ to\ P}$), 129.71 (d, Ar $C_{para\ to\ P}$), 131.43, 132.12 (d, Ar $C_{ortho\ to\ Br}$, Ar $C_{ortho\ to\ C}$), 133.51 (dd, $^2J_{PC}$ 8.9 Hz, Ar $C_{ortho\ to\ P}$), 136.53 (d, $^1J_{PC}$ 43.2 Hz, Ar $C_{ipso\ to\ P}$), 137.57 (s, Ar $C_{ipso\ to}$

C), 220.57 (d, $^2J_{PC}$ 29.1 Hz, C=O), 268.50 (d, $^2J_{PC}$ 21.7 Hz, C≡O); ^{31}P n.m.r. (101.3 MHz, $CDCl_3$) δ 71.73; *m/z* (FAB) 611/609(M^++H, 9/8), 439(M-$CH_2C_6H_4Br$, 55), 383(439-2CO, 100), 295(20), 263(37), 183(22); ν_{max} (cm^{-1}) 1903 (Fe-CO), 1607 (C=O), 1480, 1434, 1093, 919, 753, 697.

General Preparation of [(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(R)Ph] (R = Me, $CH_2OCH_2CH_2SiMe_3$, CH_2OCH_2Ph).: Butyllithium (1.2 eq) was added dropwise to an orange solution of the phenylacetyl complex **4** (1 mmol) in THF (10 ml) at -78°C and the resulting dark red solution was stirred at -78°C for 2 hrs. The halide (1.5 eq) was added and the solution stirred at -78°C for 6 hrs. The reaction was quenched with methanol (5 ml) and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and the reaction mixture was filtered through alumina (Grade V). The solvent was removed from the filtrate *in vacuo* and the crude product was purified by flash chromatography with 10% ether/hexane as eluant. Crystallisation from CH_2Cl_2/heptane furnished the α-substituted complex as orange prisms.

Preparation of (RS,RS)-*[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH($CH_2OCH_2CH_2SiMe_3$)Ph]* (RS,RS)-**13**. (Yield 82%); Found: C, 69.17; H, 6.18. $C_{38}H_{41}FeSiO_3P$ requires: C, 69.09; H, 6.25%; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ -0.02 (9H, s, $Si(CH_3)_3$), 0.84-0.95 (2H, m, $SiCH_2$), 3.08 (1H, dd, *J* 9.0, 4.4 Hz, CHCHH'), 3.34 - 3.52 (2H, m, OCH_2CH_2), 3.87 (1H, t, *J* 9.1 Hz, CHCHH'), 4.53 (5H, d *J* 0.8 Hz, C_5H_5), 4.82 (1H, dd, *J* 9.2, 4.4 Hz, CHCHH'), 7.00-7.54 (16H, m, ArH); *m/z* (FAB) 661(M^++H, 8), 439(M-CH($CH_2OCH_2SiMe_3$)Ph, 57), 383(439-2CO, 100), 263(28), 183(18), 73(20); ν_{max} (cm^{-1}) 2953, 1914 and 1903 (Fe-CO), 1609, 1482, 1435, 1250, 1092, 837, 748, 698.

Preparation of (S,S)-(-)-*[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(CH_2OCH_2Ph)Ph]* (S,S)-**14**. (Yield 78%); $[\alpha]_D$ = -41.3 (c 0.18, toluene); Found: C, 74.13; H, 5.32. $C_{40}H_{35}FeO_3P$ requires: C, 73.85; H, 5.42; ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 3.24 (1H, dd, *J* 9.0, 4.8 Hz, CHCHH'), 4.00 (1H, t, *J* 9.0 Hz, CHCHH'), 4.40, 4.51 (each 1H, d, *J* 12.0 Hz, CH_2Ph), 4.49 (5H, d *J* 1.2 Hz, C_5H_5), 4.85 (1H, dd, *J* 8.9, 4.8 Hz, CHCHH'), 7.02 - 7.04 (2H, m, $ArH_{ortho\ to\ CH}$), 7.08 - 7.12 (2H, m, $ArH_{meta\ to\ CH}$), 7.13 - 7.16 (1H, m, $ArH_{para\ to\ CH}$), 7.18 - 7.35 (20H, m, ArH); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 73.30 (t, CH_2), 73.81 (t, CH_2), 79.92 (d, CH), 85.51 (d, C_5H_5), 126.08 (d, Ar $C_{para\ to\ CH}$), 127.33 (d, Ar $C_{para\ to\ CH_2}$), 127.82 (dd, $^3J_{PC}$ 8.9 Hz, Ar $C_{meta\ to\ P}$), 127.60, 128.07, 128.20, 129.29, (d, Ar $C_{meta\ to\ CH}$, Ar $C_{meta\ to\ CH_2}$, Ar $C_{ortho\ to\ CH}$, Ar $C_{ortho\ to\ CH_2}$), 129.29 (d, Ar $C_{para\ to\ P}$), 133.37 (dd, $^2J_{PC}$ 8.8 Hz, Ar $C_{ortho\ to\ P}$), 135.99 (s, Ar $C_{ipso\ to\ CH}$), 136.78 (d, $^1J_{PC}$ 43.3 Hz, Ar $C_{ipso\ to\ P}$), 138.64 (s, Ar $C_{ipso\ to\ CH_2}$), 220.41 (d, $^2J_{PC}$ 31.9 Hz, C=O), 268.50 (d, $^2J_{PC}$ 19.7 Hz, C≡O); ^{31}P n.m.r. (101.3 MHz, $CDCl_3$) δ 73.78; *m/z* (FAB) 651(M^++H, 8), 439 (M-CH(CH_2OCH_2Ph)Ph, 54), 383(439-2CO, 100), 263(27), 183(20), 91(12); ν_{max} (cm^{-1}) 3057, 1914 (Fe-CO), 1609 (C=O), 1482, 1434, 1093, 748, 699.

Preparation of (RS,SR)-*[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(CH_3)Ph]* (RS,SR)-**15**. Found: C, 72.99; H, 5.60. $C_{33}H_{29}FeO_2P$ requires: C, 72.80; H, 5.37%; ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 1.31 (3H, d, $J_{Me,CH}$ 7.2 Hz, CH_3), 4.42 (1H, q, $J_{CH,Me}$ 7.2 Hz, CH), 4.47 (5H, d, J_{PH} 1.2 Hz, C_5H_5), 6.91-7.40 (20H, m, ArH); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 20.47 (q, CH_3), 73.87 (d, CH), 84.95 (d, C_5H_5), 125.61 (d, Ar $C_{para\ to\ C}$), 127.79 (d, Ar $C_{meta\ to\ C}$), 127.93 (dd, $^3J_{PC}$ 8.2 Hz, Ar $C_{meta\ to\ P}$), 128.61 (d, Ar $C_{ortho\ to\ C}$), 129.46 (d, Ar $C_{para\ to\ P}$), 133.43 (dd, $^2J_{PC}$ 8.4 Hz, Ar $C_{ortho\ to\ P}$), 136.73 (d, $^1J_{PC}$ 41.8 Hz, Ar $C_{ipso\ to\ P}$), 137.57 (s, Ar $C_{ipso\ to\ C}$), 220.79 (d, $^2J_{PC}$ 33.0 Hz, C=O), 275.60 (d, $^2J_{PC}$ 18.9 Hz, C≡O); ^{31}P n.m.r. (101.3 MHz,

$CDCl_3$) δ 72.85; *m/z* (FAB) 545(*M*$^+$+H, 7), 439(*M*-$CHCH_3Ph$, 55), 383(439-2CO, 100), 295(20), 263(37), 262(12), 183(22), 57(10); ν_{max} (cm^{-1}) 1903 (Fe-CO), 1607 (C=O), 1480, 1434, 1093, 919, 753, 697.

Decomposition of (RS,SR)- *and* (RS,RS)-*[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(CH_3)Ph]* (RS,SR) *-and* (RS,RS)-**15**.

(a) A nitrogen degassed solution of (*RS,SR*)- and (*RS,RS*)-**15** (5:1, 2.55 g, 4.78 mmol) and NaOMe (10 mg) in THF/MeOH (1:1, 100 ml) was stirred at room temperature under a nitrogen atmosphere for 53 hrs. The reaction mixture was concentrated *in vacuo* and flash chromatographed on silica gel with ether/hexane (1:4) as eluant to give (*RS,SR*)- and (*RS,RS*)-**15** (5:1, 2.20 g, 86%).

(b) The above diastereoisomeric mixture (2.20 g, 4.12 mmol) was dissolved in THF/MeOH (1:1, 80 ml) and stirred at room temperature open to air for 123 hrs. The reaction mixture was concentrated *in vacuo* and flash chromatographed on silica gel with ether/hexane (1:4) as eluant to give (*RS,SR*) and (*RS,RS*)-**15** (1:6, 0.15 g, 7%) as an orange oil. (*RS,RS*)-**15** ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 0.62 (3H, d, $J_{Me,CH}$ 6.7 Hz, CH_3), 4.07 (5H, d, J_{PH} 1.2 Hz, C_5H_5), 4.28 (1H, q, $J_{CH,Me}$ 6.7 Hz, CH), 7.05-7.75 (20H, m, ArH); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 18.42 (q, CH_3), 74.13 (dd, $^3J_{PC}$ 5.8 Hz, CH), 85.12 (d, C_5H_5), 126.16 (d, Ar $C_{para\ to\ C}$), 128.21 (d, Ar $C_{meta\ to\ C}$), 128.29 (dd, $^3J_{PC}$ 9.1 Hz, Ar $C_{meta\ to\ P}$), 129.21 (d, Ar $C_{ortho\ to\ C}$), 129.93 (d, Ar $C_{para\ to\ P}$), 133.49 (dd, $^2J_{PC}$ 9.6 Hz, Ar $C_{ortho\ to\ P}$), 136.84 (d, $^1J_{PC}$ 43.1 Hz, Ar $C_{ipso\ to\ P}$), 142.06 (s, Ar $C_{ipso\ to\ C}$), 221.74 (d, $^2J_{PC}$ 31.2 Hz, C=O), 277.46 (d, $^2J_{PC}$ 23.7 Hz, C≡O); ^{31}P n.m.r. (101.3 MHz, $CDCl_3$) δ 72.97; ν_{max} (cm^{-1}) 1911 (Fe-CO), 1603 (C=O), 1482, 1435, 1362, 1266, 1093, 1029, 911, 823, 752, 695.

Preparation of (RS)-*[(η^5-C_5H_5)Fe(CO)(PPh_3)COCHPh_2]* (RS)-**16**. Butyllithium (1.2 eq) was added dropwise to an orange solution of the acetyl complex (*RS*)-**4** (3.36 g, 6.34 mmol) in THF (60 ml) at -78°C and the resulting dark red solution was stirred at -78°C for 1 hr. The solution was then cooled to -100°C and a precooled (-100°C) solution of the bromotosylate **6** (1.48 g, 4.53 mmol) was added *via* cannula, followed immediately by the dropwise addition of BuLi (1 eq), such that the temperature of the reaction mixture did not exceed -95°C. The solution was allowed to warm to -78°C and stirred at this temperature for 1 hr. The reaction was quenched with methanol (5 ml) and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and the reaction mixture was filtered through alumina (Grade V). The solvent was removed *in vacuo* and the crude product was purified by flash chromatography with ether/hexane (1:4) as eluant affording in order of increasing polarity; (i) (*RS*)-**16** (1.62 g, 59%) as an orange solid; Found: C, 75.53; H, 5.47. $C_{38}H_{31}FeO_2P$ requires: C, 75.25; H, 5.16%; ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 4.21 (5H, d, *J* 1.3 Hz, C_5H_5), 5.88 (1H, s, $CHPh_2$), 6.83 - 7.48 (25 H, m, ArH); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 85.06 (d, C_5H_5), 86.21 (dd, $^3J_{PC}$ 4.6 Hz, $CHPh_2$), 125.62 (d, Ar $C_{para\ to\ C}$), 126.37 (d, Ar $C_{para\ to\ C}$), 127.73 (d, Ar $C_{meta\ to\ C}$), 128.19 (dd, $^3J_{PC}$ 7.9 Hz, Ar $C_{meta\ to\ P}$), 128.38 (d, Ar $C_{meta\ to\ C}$), 128.67 (d, Ar $C_{ortho\ to\ C}$), 129.70 (d, Ar $C_{para\ to\ P}$), 129.81 (d, Ar $C_{ortho\ to\ C}$), 133.33 (dd, $^2J_{PC}$ 8.0 Hz, Ar $C_{ortho\ to\ P}$), 136.48 (d, $^1J_{PC}$ 43.0 Hz, Ar $C_{ipso\ to\ P}$), 140.25 (s, Ar $C_{ipso\ to\ C}$), 140.45 (s, Ar $C_{ipso\ to\ C}$), 220.97 (d, $^2J_{PC}$ 30.8 Hz, C=O), 271.58 (d, $^2J_{PC}$ 21.6 Hz, C≡O); ^{31}P n.m.r. (101 MHz, $CDCl_3$) δ 72.33; *m/z* 607(*M*$^+$+H, 6), 578(*M*-CO, 2), 383(*M*-8-$COCHPh_2$, 100), 288(30), 263(39), 183(24), 167(21), 152(19), 135(21), 119(25); ν_{max} (cm^{-1}) 1915 (Fe-CO), 1588 (C=O), 1580, 1481, 1451, 1435, 1083, 736, 698; this compound is very unstable in solution decomposing readily into a number of products including [$(C_5H_5)Fe(CO)_2(PPh_3)]^+$ [ν_{max} (cm^{-1}) 2052 and 2008 (Fe-CO)]; and (ii) recovered (*RS*)-**4** (1.57 g).

Preparation of 2-Bromo-2-phenethyl benzyl bromide **17**. *N*-Bromosuccinimide (1.2 eq) was added to a solution of the iron complex **14** (250 mg, 0.38 mmol) in dichloromethane (5 ml) at -78°C. The solution was then allowed to warm slowly to room temperature, and the dark green solution was stirred for 30 min. The solvent was removed *in vacuo* and the crude product was purified by radial chromatography with 5% ether/petrol as eluant. The solvent was removed *in vacuo* to give the bromide **17** (82 mg, 76%) as an oil; ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.94 (1H, dd, *J* 10.5, 6.9 Hz, CHCHH'), 4.00 (1H, dd, *J* 10.7, 7.3 Hz, CHCHH'), 4.60, 4.57 (each 1H, d, *J* 12.2 Hz, $PhCH_2O$), 5.09 (1H, t, *J* 7.0 Hz, CH), 7.39 - 7.26 (5H, m, ArH); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 51.85 (d, CH), 73.26 (t, OCH_2), 74.38 (t, OCH_2), 127.68, 127.77, 127.91, 128.41, 128.65 (d, Ar CH) 137.76, 139.23 (s, Ar C_{ipso}); *m/z* (CI) 310/308(M^+, 7/7), 193(8), 181(27), 169(8), 108 (13), 104 (24), 92 (11), 91 (100).

Preparation of a solution of chlorine gas in dichloromethane. A stream of chlorine gas was bubbled into dichloromethane and then an aliquot was taken and quenched with aqueous NaI solution. Approximate chlorine concentration was determined by titration with 0.1*M* sodium thiosulphate solution of the iodine formed on addition of sodium iodide.

(S)-(-)-Methyl Tropinate Benzyl Ether (S)-**18** To a solution of *(S,S)*-**14** (500 mg, 0.92 mmol) in 1:1 THF/methanol (5 ml) at -100° under an atmosphere of nitrogen was added dropwise to 1 eq of a pretitrated solution of chlorine gas in CH_2Cl_2. The dark green solution was stirred at -100° for 30 minutes, and the reaction mixture was then thoroughly degassed to remove excess chlorine. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and fritted on alumina (Grade V). The solvent was removed from the filtrate *in vacuo* and the crude product was purified by radial chromatography with 10% ether/petrol as eluant. The product (*S*)-**18** was obtained as an oil (148 mg, 72%); $[\alpha]_D^{23}$ = -49.9 (c 1.00, $CHCl_3$); H.R.M.S: Found: 270.1253. $C_{17}H_{18}O_3$ requires: 270.1256; ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 3.67 (1H, dd, *J* 9.8, 5.0 Hz, CHCHH'), 3.71 (3H, s, OCH_3), 3.94 (1H, dd, *J* 9.4, 5.1 Hz, CHCHH'), 4.07 (1H, t, *J* 9.2 Hz, $CHCH_2$), 4.53, 4.58 (each 1H, d, *J* 12.2 Hz, $PhCH_2O$), 7.26 – 7.36 (10H, m, ArH); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 51.98 (q, OCH_3), 51.98 (d, CH), 71.60 (t, OCH_2), 73.13 (t, OCH_2), 127.65, 128.12, 128.36, 128.73 (d, Ar CH), 137.73, 138.01 (s, Ar C_{ipso}), 172.98 (s, C=O); *m/z* (CI) 288(M^++NH_4, 17), 271(M^++H, 40), 270 (M^+, 15), 253(28), 240(20), 181(16), 150(21), 137(17), 121(18), 118(21), 108(23), 104(25), 92(19), 91 (100), 65(14); ν_{max} (cm^{-1}) 3063, 3031, 2951, 2865, 1734, 1603, 1497, 1454, 1435, 1361, 1204, 1166, 1090, 1029, 853, 738, 699, 622.

(S)-(-)-Methyl Tropinate (S)-**2**. To a solution of the benzyl ether (*S*)-**18** (100 mg, 0.37 mmol) in methanol (3 ml) was added 10% palladised carbon (10 mg) and glacial acetic acid (5 drops) and the solution was stirred under an atmosphere of hydrogen for 24 hrs. The mixture was filtered through Celite, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give (*S*)-(-)-methyl tropinate (*S*)-**2** (63 mg, 94%) as an oil, $[\alpha]_D^{23}$ = -69.8 (c 0.875, Me_2CO) lit.[16] -69.9 (c 4.947 in Me_2CO), ^{1}H n.m.r. (500 MHz, $CDCl_3$) δ 3.72 (3H, s, OCH_3), 3.87 - 3.82 (2H, m, $CHCH_2$), 4.15 (1H, dd *J* 10.4, 7.9 Hz, $CHCH_2$), 7.27 - 7.35 (5H, m, ArH); ^{13}C n.m.r. (125 MHz, $CDCl_3$) δ 52.08 (q, OCH_3), 53.97 (d, $CHCH_2$), 64.52 (t, OCH_2), 127.70 (d, Ar C_{para}), 128.13, 128.83 (d, Ar C_{ortho}, Ar C_{meta}), 135.64 (s, Ar C_{ipso}), 173.54 (s, C=O); *m/z* (CI) 198(M^++NH_4, 48), 195(M^++H, 18), 182(21), 181(100), 180(23), 163(30), 151(50), 150

(84), 121(27), 118(61), 104(16), 103(15), 91(46), 90(20); ν_{max} (cm^{-1}) 3830, 3022, 2981, 2964, 2869, 1735, 1601, 1166, 1042, 737, 695.

References

1. T.Y. Shen, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 460.
2. J.-P. Rieu, A. Boucherle, H. Cousse and G. Mouzin, *Tetrahedron*, 1986, **42**, 4095.
3. Merck Index, Eleventh Ed., S. Budavari, Ed., Merck & Co., Inc., pp 138, 773; and references cited therein.
4. P. Newman, *Optical Resolution Procedures for Chemical Compounds*, Optical Resolution Information Centre, New York, Vol. 2, Part 1, 391.
5. S.G. Davies, *Aldrichimica Acta*, 1990, **23**, 31.
6. S.L. Brown, S.G. Davies, D.F. Foster, J.I. Seeman and P. Warner, *Tetrahedron Lett.*, 1986, **27**, 623.
7. Z.-W. Guo and A. Zamojski, *Tetrahedron Lett.*, 1992, **33**, 1105.
8. R.W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Acadaemic Press, New York, 1967; M.-C. Carre, B. Gregoire and P. Caubere, *J. Org. Chem.*, 1984, **49**, 2050 and references therein.
9. R.W. Baker, T.M. Baker, A.A. Birkbeck, R.G.F. Giles, M.V. Sargent, B.W. Skelton and A.H. White, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1589.
10. S.G. Davies and J.I. Seeman, *Tetrahedron Lett.*, 1984, **25**, 1845.
11. D. Crich and L.B.L. Lim, *Synlett*, 1990, **1**, 117.
12. T. Benneche, P. Strande and K. Undheim, *Synthesis*, 1983, 762.
13. S.G. Davies, I.M. Dordor, J.C. Walker and P. Warner, *Tetrahedron Lett.*, 1984, **25**, 2709.
14. S.G. Davies, R.J.C. Easton, J.C. Walker and P. Warner, *Tetrahedron*, 1986, **42**, 175.; F. Stolz, P. Strazewski, C. Tamm, M. Neuburger and M. Zehnder, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 193.
15. L.S. Liebeskind, M.E. Welker and R.W. Fengl, *J. Am. Chem. Soc.*, 1986, **108**, 6328.
16. A. MacKenzie and E.R. Winton, J. Chem. Soc., 1940, 840; see also M.B. Watson and G.W. Youngson, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1597.
17. D.F. Shriver and M.A. Drezdon, *The Manipulation of Air Sensitive Compounds*, Wiley Interscience, New York, 1986.
18. Oxford Asymmetry Ltd, 57, Milton Park, Abingdon, Oxon, OX14 4RX, U.K.
19 D.J. Watkin, J.R. Carruthers and P.W. Betteridge, *Crystals User Guide*, Chemical Crystallography Laboratory, Oxford, 1985.
20 A. North, D.C. Phillips and D. Matthews, *Acta Cryst*, 1968, **A24**, 351.
21 G.M. Sheldrick, *Crystallographic Computing 3*, Oxford University Press, 1985.