Tetrahedron: Asymmetry Vol. 2, No. 10, pp. 1075-1082, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Asymmetric Syntheses of Ethyl (S)-(+)-2-Methylhept-4-ynoate Using Both Enantiomers of the Chiral Iron Auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$.

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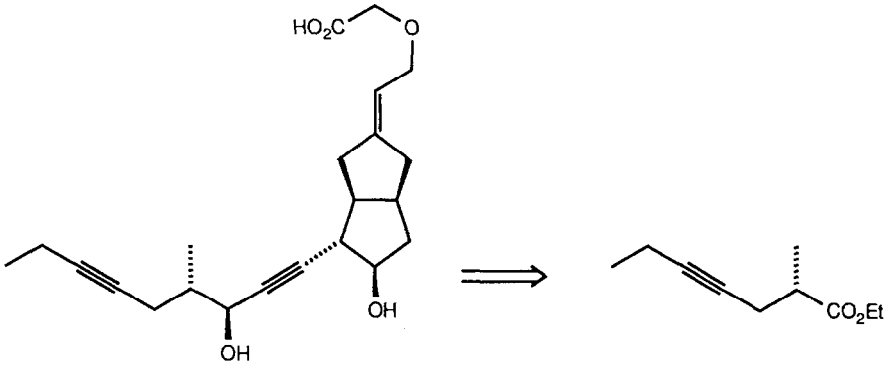
(*Received* 22 *August* 1991)

Abstract: The asymmetric syntheses of ethyl (S)-(+)-2-methylhept-4-ynoate *via* double alkylations of the homochiral acetate equivalents (R)- and (S)-$[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_3]$ are described.

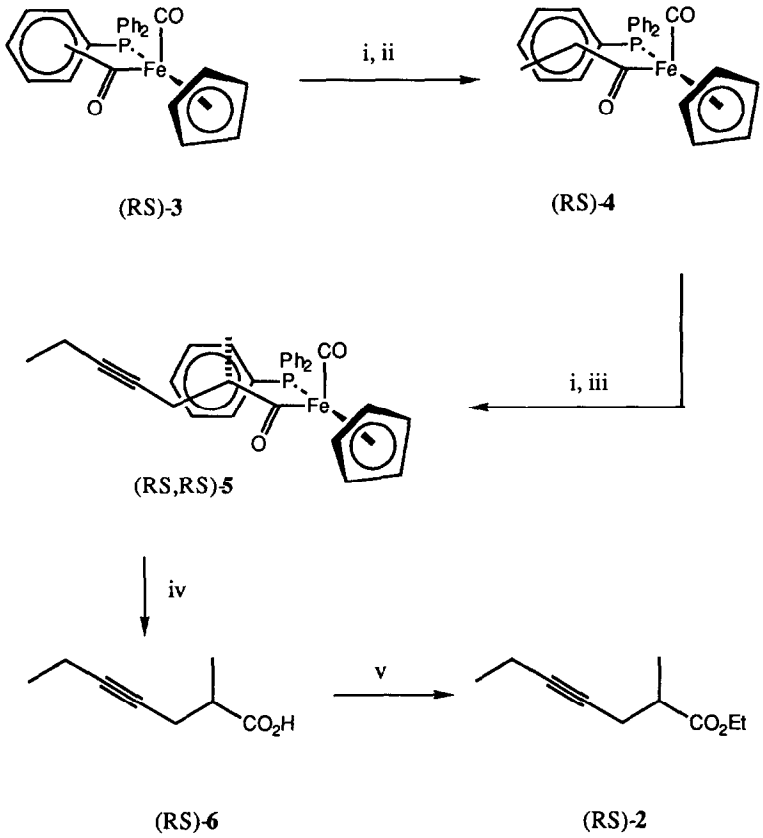
The metabolically stable analogue of prostacyclin, ZK96480 **1**, exhibits activity as a vasodilator and inhibits the formation of blood platelets.[1,2] The first synthesis of this compound was reported[1,2] in 1980, while an improved synthesis of the key intermediate for the sidechain of **1**, ethyl (S)-(+)-2-methylhept-4-ynoate **2** appeared in 1989.[3] This latter synthesis involved the alkylation of the chiral propanoyl enolate derived from Evans' chiral auxiliary (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone, however the stereoselectivity was low (d.e. 72%).



ZK96480 **1** (S)-(+)-**2**

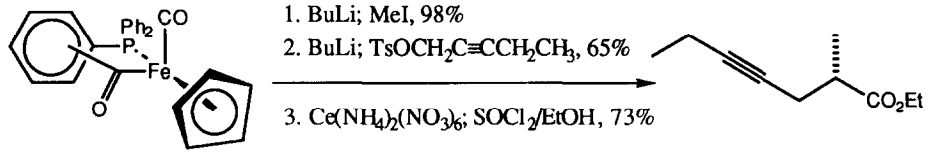
We have previously reported the highly stereoselective double alkylation reactions, *via* enolate intermediates, of the chiral iron acetyl complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_3]$ **3**.[4] For a particular double alkylation process the diastereoisomer produced is determined by the order of the alkylation steps and hence by inverting this order a particular absolute configuration of the newly formed stereogenic centre may be obtained either from (R)-**3** or from (S)-**3**. Thus ethyl (S)-(+)-2-methylhept-4-ynoate **2** should be available, after decomplexation, from (S)-**3** *via* sequential methylation and pent-2-ynylation or from (R)-**3** *via* sequential pent-2-ynylation and methylation. We describe here the successful application of each of these processes firstly in the racemic series and then in each homochiral series.

Deprotonation of the racemic iron acetyl complex (RS)-**3** with butyl lithium and quenching the thus formed enolate with methyl iodide generated the iron propanoyl derivative (RS)-**4** in 98% yield.[5] Alkylation of the enolate derived from (RS)-**4** with pent-2-ynyl tosylate[6] stereoselectively generated (RS,RS)-**5**.[7] ^{1}H nmr spectroscopic analysis of the crude product clearly showed the diastereoisomeric excess to be 94%. Pure (RS,RS)-**5** could be obtained by a single crystallisation (yield 50%) or by column chromatography (yield 67%). The configuration of the new α-stereogenic centre relative to that of the iron centre was assigned on the basis of the characteristic ^{1}H nmr chemical shift (δ 0.36) of the α-methyl group.[8] Decomplexation of crude (RS,RS)-**5** with aqueous ceric ammonium nitrate gave racemic (RS)-2-methylhept-4-ynoic acid (RS)-**6**, which was esterified without purification to give the racemic ethyl ester (RS)-**2** in 88% yield from **5**.



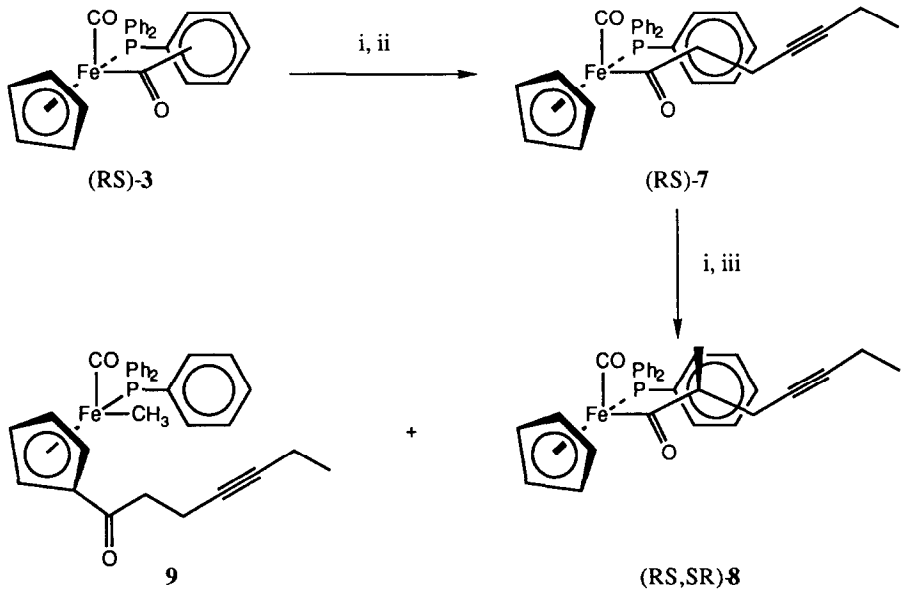
Reagents. i) BuLi; ii) MeI; iii) $TsOCH_2C{\equiv}CCH_2CH_3$; iv) $Ce(NH)_4(NO_3)_6$; v) $SOCl_2$ / EtOH.

Starting from the homochiral iron acetyl complex (S)-**3**[9] sequential methylation and pent-2-ynylation gave after chromatography of the crude product (d.e. 94%) diastereoisomerically pure (S,S)-**5** in 64% yield. Oxidative decomplexation to the acid (S)-**6** followed by esterification gave homochiral ethyl (S)-(+)-2-methylhept-4-ynoate **2** in 73% yield {$[\alpha]_D^{20}$ +8.4 (*c* 1.00 in $CHCl_3$); Lit.[3] $[\alpha]_D^{20}$ +8.4 (*c* 1.00 in $CHCl_3$)}.



(S)-**3** (S)-(+)-**2** overall yield 47%

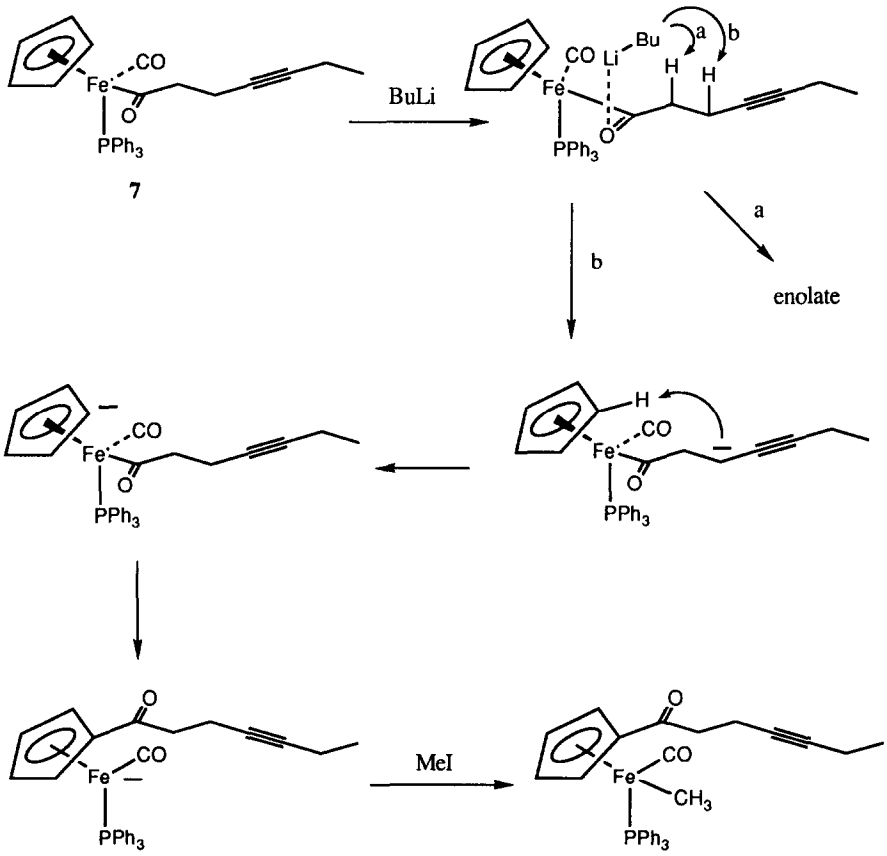
Reaction of the lithium enolate derived from the racemic acetyl complex (RS)-**3** with pent-2-ynyl tosylate[6] gave the hept-4-ynoyl complex (RS)-**7** in 85% yield. This, deprotonation with butyl lithium followed by quenching of the thus formed enolate with methyl iodide, gave the required α-methylated complex (RS,SR)-**8** with a diastereoisomeric excess >98% together with complex **9** in the ratio 90 : 10. Chromatography gave pure (RS,SR)-**8** in 82% yield. The configuration of the new α-stereogenic centre in **8** relative to that of the iron centre was assigned on the basis of the characteristic ^1H nmr shift (δ 1.15) of the α-methyl group.[8]



(RS)-**3** (RS)-**7** **9** (RS,SR)-**8**

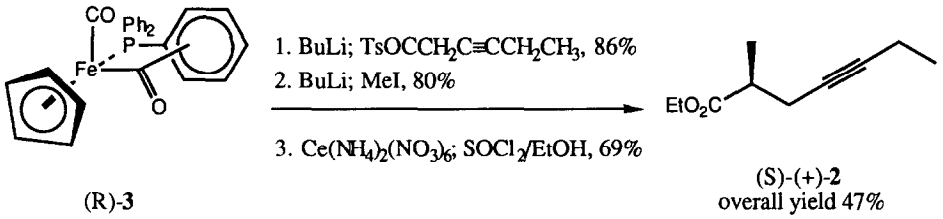
Reagents. i) BuLi; ii) $TsOCH_2C{\equiv}CCH_2CH_3$; iii) MeI.

It has already been reported[3] that the methylation of **7** yields a similar mixture (89 :11) of products however the minor product was assigned without justification as the unwanted diastereoisomer **5**. In our mixture (90 : 10) the minor product is certainly not the unwanted diastereoisomer since we had **5** to hand for a direct comparison. On the basis of its red-colour and ^1H nmr spectroscopic analysis the minor product was assigned as the rearranged complex **9**. Of particular note in the nmr spectrum of **9** was the characteristic iron methyl doublet observed at δ -0.10 (J_{PH} 5.6 Hz) and the AA'MM' coupled system for the four cyclopentadienyl hydrogens. Whilst this type of rearrangement has not been observed before at -78°C[10] it is common when iron acyl complexes of this type are deprotonated at higher temperatures, deprotonation of the cyclopentadienyl ring competing with enolate formation. After cyclopentadienyl ring deprotonation migration of the acyl group to the cyclopentadienyl is rapid thus generating an anionic iron centre which is methylated on methyl iodide quench. A consistent explanation for the formation of **9** above is therefore that on treatment of **7** with butyl lithium there is a competition between α-deprotonation to form the enolate and β-deprotonation to form the propargyl anion. Both deprotonation routes would be favoured by prior chelation of the base to the acyl oxygen. The propargyl anion is ideally set up to intramolecularly abstract a proton from the cyclopentadienyl ligand thus allowing acyl migration to occur. Finally methyl iodide quench would generate **9.**



7 **9**

Starting from the homochiral iron acetyl complex (R)-3[9] sequential pent-2-ynylation and methylation gave after chromatography diastereoisomerically pure (R,S)-**8** in 69% yield. Removal of the auxiliary with ceric ammonium nitrate and esterification of the thus formed acid (S)-**6** gave the desired homochiral ethyl (S)-(+)-2-methylhept-4-ynoate **2** in 69% yield {$[\alpha]_D^{20}$ +8.4 (*c* 1.00 in $CHCl_3$); Lit.[3] $[\alpha]_D^{20}$ +8.4 (*c* 1.00 in $CHCl_3$)}.



(R)-3

(S)-(+)-2
overall yield 47%

In conclusion we have demonstrated that homochiral ethyl (S)-(+)-2-methylhept-4-ynoate **2**, a key intermediate in the synthesis of ZK96480, can be prepared from either enantiomer of the chiral iron acetyl complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_3]$ **3** by sequential alkylations and decomplexation. The overall yield for both routes is coincidentally 47%.

Experimental:

General-All reactions and purifications involving organometallic compounds were carried out under an atmosphere of nitrogen using vacuum line and Schlenk tube techniques[11] and all solvents were deoxygenated. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Light petroleum refers to the fraction boiling in the range 40 - 60°C. Butyllithium was used as a 1.4 or 1.6 mol dm^{-3} solution in hexane. Methyl iodide was dried over 4Å molecular sieves. All other reagents were used as received. Flash chromatography was performed on silica (43-60μm) under a positive nitrogen pressure.

^1H NMR spectra were recorded on a Bruker WM-300 spectrometer operating at 300.13 MHz using $CDCl_3$ as solvent and referenced to residual $CHCl_3$ with chemical shifts being reported as δ ppm from TMS. ^{13}C NMR spectra were recorded on a Bruker AM-250 spectrometer operating at 62.90 MHz using $CDCl_3$ as solvent and internal reference and chemical shifts are reported as δ ppm from TMS. ^{31}P NMR spectra were recorded on a Bruker AM-250 spectrometer operating at 101.26 MHz using $CDCl_3$ as solvent and chemical shifts are reported as δ ppm from an external reference of triethyl phosphate in D_2O. *J* values are reported in Hz. IR spectra were obtained as chloroform solutions im 1 mm cells on a Perkin-Elmer 297 instrument calibrated against polystyrene (1601 cm^{-1}). Mass spectra were recorded on a V.G. Micromass ZAB 2F instrument using electron impact and chemical ionisation techniques. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Dyson Perrins Laboratory Analytical Service. Melting points were measured in sealed, nitrogen filled capillaries using a Kofler hot-stage apparatus and are uncorrected.

Preparation of [(RS,RS)-(η^5-C_5H_5)Fe(CO)(PPh_3)C(O)CH(CH_3)CH_2C≡CCH_2CH_3] **5**. - To a -78 °C solution of (RS)-**4**[5] (1.16 g, 2.48 mmol) in tetrahydrofuran (20 ml) was added BuLi (2.5 mmol) and, after stirring for 1 h, the tosylate of 2-pentyn-1-ol (700 mg, 2.94 mmol) was added neat. The solution was stirred for 8 h at -78 °C and then overnight at room temperature. The reaction was quenched with methanol (1 ml) and the solvent was removed. The residue was preadsorbed and chromatographed on silica (CH_2Cl_2) to yield complex **5** as an orange solid (888 mg, 67 %), m.p. 145-146 °C (Found: C, 71.5; H, 6.1. $C_{32}H_{31}FeO_2P$ requires C, 71.9; H, 5.9); ν_{max}/cm^{-1} 1910 (C≡O), 1590 (C=O); δ_H 7.57 - 7.50 (6 H, m, ArH_{ortho}), 7.39 - 7.33 (9 H, m, ArH_{meta} and ArH_{para}), 4.49 (5 H, d, *J* 1.2, C_5H_5), 3.03 - 2.97 (1 H, m, COC*H*), 2.46 - 2.37 (1 H, m, C*H*H'C≡CCH_2CH_3), 2.27 - 2.12 (3 H, m, CH*H'*C≡CCH_2CH_3), 1.11 (3 H, t, *J* 7.5, CH_2CH_3), 0.36 (3 H, d, J 6.7, $CHCH_3$); δ_C 278.41 (d, J_{PC} 22.0, C=O), 220.86 (d, J_{PC} 30.6, C≡O), 136.64 (d, J_{PC} 42.4, Ar C_{ipso}), 133.51 (dd, J_{PC} 9.5, Ar C_{ortho}), 129.65 (d, Ar C_{para}), 127.98 (dd, J_{PC} 9.4, Ar C_{meta}), 85.40 (d, C_5H_5), 82.61, 78.50 (s, C≡C), 65.42 (dd, J_{PC} 5.6, COCH), 22.47 (t, CH_2C≡CCH_2CH_3), 14.96, 14.30 (q, CH_3), 12.50 (t, CH_2CH_3); δ_P 71.14; *m/z* 535 (M^+ + 1).

Further elution afforded starting material **4** (104 mg, 9 %).

Preparation of [(S,S)-(η^5-C_5H_5)Fe(CO)(PPh_3)C(O)CH(CH_3)CH_2C≡CCH_2CH_3] **5**. - The above procedure was repeated using homochiral (S)-**4** (2.56 g, 5.47 mmol), BuLi (6.0 mmol) and the tosyltate of 2-pentyn-1-ol (1.67 g, 7.01 mmol). Complex (S,S)-**5** was obtained as an orange solid (1.90 g, 65 %), m.p. 139-140 °C (CH_2Cl_2-hexane) (Found: C, 71.1; H, 6.0. $C_{31}H_{29}FeO_2P$ requires C, 71.9; H, 5.9); $[\alpha]_D^{20}$ +149.3 (*c* 0.15 in $CHCl_3$). The spectroscopic properties were identical to those listed above.

Preparation of [(RS)-(η^5-C_5H_5)Fe(CO)(PPh_3)C(O)CH_2CH_2C≡CCH_2CH_3] **7**. - To a -78 °C solution of (RS)-**3** (500 mg, 1.10 mmol) in tetrahydrofuran (10 ml) was added BuLi (1.1 mmol) and, after stirring for 1 h, the tosylate of 2-pentyn-1-ol (286 mg, 1.20 mmol) was added neat. The solution was stirred for 8 h at -78 °C and then overnight at room temperature. The reaction was quenched with methanol (1 ml) and the solvent was removed. The residue was preadsorbed and chromatographed on silica (CH_2Cl_2) to yield complex **7** as an orange solid (484 mg, 85 %), m.p. 138-139 °C (CH_2Cl_2-hexane) (Found: C, 71.2; H, 5.9. $C_{31}H_{29}FeO_2P$ requires C, 71.5; H, 5.6); ν_{max}/cm^{-1} 1910 (C≡O), 1600 (C=O); δ_H 7.52 - 7.46 (6 H, m, ArH_{ortho}), 7.40 - 7.33 (9 H, m, ArH_{meta} and ArH_{para}), 4.43 (5 H, d, *J* 0.7, C_5H_5), 3.10 (1 H, ddd, *J* 16.9, 9.2, 6.2, COC*H*H'), 2.73 (1 H, ddd, *J* 16.9, 8.9, 5.4, COCH*H'*), 2.18 - 2.06 (3 H, m, C*H*H'C≡CCH_2CH_3), 1.70 (1 H, m, CH*H'*C≡CH_2CH_3), 1.10 (3 H, t, *J* 7.4, CH_3); δ_C 274.06 (d, J_{PC} 23.2, C=O), 220.39 (d, J_{PC} 31.1, C≡O), 136.43 (d, J_{PC} 43.3, Ar C_{ipso}), 133.29 (dd, J_{PC} 9.8, Ar C_{ortho}), 129.68 (d, Ar C_{para}), 128.01 (dd, J_{PC} 9.8, Ar C_{meta}), 85.21 (d, C_5H_5), 81.14, 79.73 (s, C≡C), 63.93 (dd, J_{PC} 3.5, COCH), 14.33 (t, CH_2C≡CCH_2CH_3), 14.33 (q, CH_3), 12.47 (t, CH_2CH_3); δ_P 72.63; *m/z* 521 (M^+ + 1).

Further elution afforded starting material **3** (53 mg, 11 %).

Preparation of [(R)-(η^5-C_5H_5)Fe(CO)(PPh_3)C(O)CH_2CH_2C≡CCH_2CH_3] **7**. - The above procedure was repeated using homochiral (R)-**3** (1.78 g, 3.92 mmol), BuLi (4.0 mmol) and the tosylate of 2-pentyn-1-ol (1.07 g, 4.50 mmol). Complex (R)-**7** was obtained as an orange solid (1.75 g, 86 %), m.p. 142-144 °C (CH_2Cl_2-hexane) (Found: C, 71.4; H, 5.8. $C_{31}H_{29}FeO_2P$ requires C, 71.5; H, 5.6); $[\alpha]_D^{20}$ -99.4 (*c* 0.17 in $CHCl_3$). The spectroscopic properties were identical to those listed above.

Preparation of [(RS,SR)-(η^5-C_5H_5)Fe(CO)(PPh_3)C(O)CH(CH_3)CH_2C≡CCH_2CH_3] **8**. - To a -78 °C solution of (RS)-**4** (163 mg, 0.313 mmol) in tetrahydrofuran (25 ml) was added BuLi (0.4 mmol) and the solution was stirred for 1 h. MeI (excess) was added, stirring was continued for 15 min and the reaction was quenched with methanol (1 ml). The solvent was removed and the residue was preadsorbed and chromatographed on silica using CH_2Cl_2-light petroleum (4:1). Eluted first was complex **9** as a highly viscous red oil (13 mg, 8 %); (Found: C, 71.7; H, 5.7. $C_{31}H_{29}FeO_2P$ requires C, 71.9; H, 5.9); ν_{max}/cm^{-1} 1915 (C≡O), 1658 (C=O); δ_H 7.45 - 7.30 (15 H, m, Ar*H*), 5.27 - 5.24, 5.00 - 4.97, 4.20 - 4.15, 4.01 - 3.96 (1 H, m C_5H_4), 2.85 - 2.77, 2.58 - 2.47 (2 H, m, CH_2CH_2), 2.22 - 2.07 (2 H, m, C≡CCH_2CH_3), 1.10 (3 H, t, *J* 7.4, CH_2CH_3), -0.10 (3 H, d, J_{PH} 5.6, FeCH_3); *m/z* 535 (M^+ + 1).

Eluted next was complex **8** as an orange solid (116 mg, 69%), m.p. 157-159 °C (CH_2Cl_2-hexane) (Found: C, 71.8; H, 6.2. $C_{31}H_{29}FeO_2P$ requires C, 71.9; H, 5.9); ν_{max}/cm^{-1} 1920 (C≡O), 1585 (C=O); δ_H 7.52 - 7.46 (6 H, m, ArH_{ortho}), 7.40 - 7.35 (9 H, m, ArH_{meta} and ArH_{para}), 4.46 (5 H, d, *J* 1.0, C_5H_5), 2.85 - 2.79 (1 H, m, COC*H*), 2.16 - 2.07 (2 H, m, CH_2CH_3), 1.61 - 1.50 (2 H, m, CH_2C≡CCH_2CH_3), 1.15 (3 H, d, J 7.2, CHCH_3), 1.09 (3 H, t, *J* 7.5, CH_2CH_3); δ_C 278.90 (d, J_{PC} 23.1, C=O), 220.80 (d, J_{PC} 31.7, C≡O), 136.38 (d, J_{PC} 42.4, Ar C_{ipso}), 133.31 (dd, J_{PC} 9.8, Ar C_{ortho}), 129.80 (d, Ar C_{para}), 128.12 (dd, J_{PC} 9.6, Ar C_{meta}), 83.77 (d, C_5H_5), 82.11, 79.33 (s, C≡C), 65.33 (dd, J_{PC} 6.0, COCH), 21.39 (t, CH_2C≡CCH_2CH_3), 16.10, 14.45 (q, CH_3), 12.54 (t, CH_2CH_3); δ_P 70.56; *m/z* 535 (M^+ + 1).

Preparation of [(R,S)-(η^5-C_5H_5)Fe(CO)(PPh_3)C(O)CH(CH_3)CH_2C≡CCH_2CH_3] **8**. - The above procedure was repeated using homochiral (R)-**7** (1.19 g, 2.29 mmol) and BuLi (2.5 mmol). Complex (R,S)-**8** was obtained as an orange solid (978 mg, 80 %), m.p. 153-155 °C (CH_2Cl_2-hexane) (Found: C, 71.9; H, 6.1. $C_{31}H_{29}FeO_2P$ requires C, 71.9; H, 5.9); $[\alpha]_D^{20}$ -50.4 (*c* 0.23 in $CHCl_3$). The spectroscopic properties were identical to those listed above.

Preparation of (RS)-*ethyl 2-methylhept-4-ynoate* **2**. - A solution of complex (RS,RS)-**5** (646 mg, 1.21 mmol) or (RS,SR)-**8** (1.31 g, 2.45 mmol) and ceric ammonium nitrate (5 equivalents) in wet tetrahydrofuran (15 ml) was stirred overnight at room temperature. The solvent was removed and the sticky residue was triturated vigourously for 15 min in a mixture of 5% NaOH solution (50 ml) and ether (50 ml). The organic layer was separated and the aqueous layer acidified with concentrated HCl solution before being extracted with another portion of ether. The combined organic layers were dried and concentrated to give the crude acid **6** as an acrid smelling viscous yellow oil. This was dissolved in ethanol (20 ml) and thionyl chloride (3 -5 equivalents) was added dropwise. After stirring for 1 h the solvent was removed and the residue was chromatographed on silica using CH_2Cl_2-light petroleum (1:9) as eluent. The product was further purified by Kugelrohr distillation, which afforded the product **2** as a colourless liquid (179 mg, 88% from **5**; 309 mg, 75 % from **8**), ν_{max}/cm^{-1} 1720 (lit.[3] 1718); δ_H 4.15 (2 H, q, *J* 7.1, OCH_2), 2.64 - 2.53 (1 H, m, COC*H*), 2.49 (1 H, ddt, *J* 16.3, 6.0, 2.3, C*H*H'C≡CCH_2CH_3), 2.31 (1 H, ddt, *J* 16.3, 7.6, 2.3, CH*H'*C≡CCH_2CH_3), 2.15 (2 H, qt, *J* 7.5, 2.3, C≡CCH_2CH_3), 1.27 (3 H, t, *J* 7.1, OCH_2CH_3), 1.24 (3 H, d, *J* 6.9, CHCH_3), 1.11 (3 H, t, *J* 7.5, C≡CCH_2CH_3); δ_C 175.20 (s, CO_2Et), 60.36 (t, OCH_2), 39.34 (d, COCH), 23.08 (t, CH_2C≡CCH_2CH_3), 16.31, 14.19 (q, 3 x CH_3), 12.36 (t, C≡CCH_2CH_3); *m/z* 168 (M^+).

Preparation of (S)-*ethyl 2-methylhept-4-ynoate* **2**. - The above procedure was repeated using homochiral (S,S)-**5** (1.44 g , 2.69 mmol) and (R,S)-**8** (759 mg, 1.42 mmol) which afforded the homochiral ester (S)-(+)-**2** (330 mg, 73% from **5**; 165 mg, 69% from **8**), $[\alpha]_D^{20}$ +8.4 (*c* 1.00 in $CHCl_3$) (lit.[3] +8.4). The spectroscopic properties were identical to those listed above.

Acknowledgements:
The authors gratefully acknowledge financial support from the S.E.R.C. and the N.S.E.R.C. of Canada (G.J.B.).

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