Asymmetric Synthesis of (−)-Actinonin and (−)-*epi*-Actinonin

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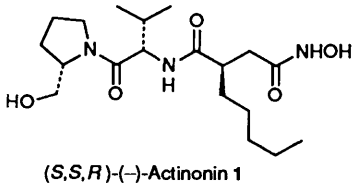
The highly asymmetric induction imparted by the iron chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ is exploited in the preparation of homochiral (*R*)- and (*S*)-α-pentylsuccinates. Their application in the synthesis of (−)-actinonin and (−)-*epi*-actinonin is described.

The continued search towards understanding the mechanism for the propagation of malignant cancer cells has recently implicated the direct involvement of the zinc-based proteolytic enzyme collagenase, which catalyses the breakdown of the basement membrane of healthy cells, allowing the invasion of malignant cells.[1] Other zinc-based proteases have also recently been shown to take part in enzyme-catalysed cascades causing several types of disorders in humans, of which arthritis and hypertension are two examples.[2]

Studies by high-resolution X-ray crystallographic methods, as well as investigations concerning the chemical processes involved in breaking peptide bonds by these zinc proteases, have revealed the location of their active site and also the essential stereochemical features and electrostatic environment under which they function.[3] This has led to the elucidation of the mechanism by which natural enzyme inhibitors function and, subsequently, to the development of specifically designed drugs and their analogues which bind irreversibly to the active sites of several types of enzymes, thus blocking their activity.[4]

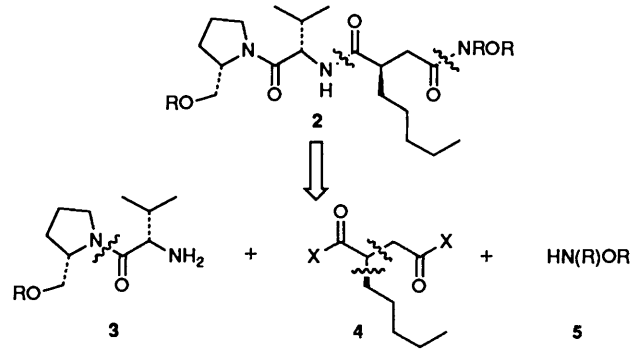
Actinonin **1**, a natural pseudopeptide, has been shown to be a potent *in vivo* inhibitor of collagenase.[5] The primary features of this compound are its hydroxamic acid functionality, the α-alkylsuccinate backbone and the amino acid-derived unit. The hydroxamic acid is thought to associate with the zinc centre of the enzyme, forming a stable tetrahedral complex, while the succinic and amino acid fragments are responsible for the recognition and binding of the inhibitor to the active site.



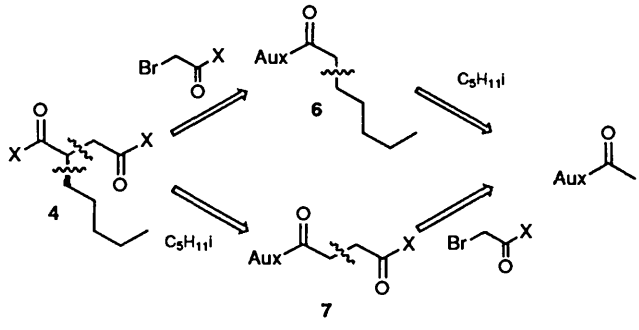
(*S,S,R*)-(−)-Actinonin **1**

Although (−)-actinonin is available from cultures of *Streptomyces* and *Actinomyces* bacteria,[6] it is necessary to have easy access to sufficient quantities of compounds structurally related to known examples such as actinonin in order fully to investigate the optimum structure–activity relationship for collagenase inhibitors. A previous nonstereoselective synthetic procedure produced (*S,S,R*)-(−)-actinonin **1** only in low yield, principally due to an inefficient separation of diastereoisomers,[7] and was therefore unsuitable for the synthesis of analogues. We describe here the asymmetric synthesis of (*S,S,R*)-(−)-actinonin and (*S,S,S*)-(−)-*epi*-actinonin. Part of this work has been previously communicated.[8]

Our synthetic strategy towards (−)-actinonin involves the independent syntheses of the three fragments **3**, **4** and **5** in suitably protected and/or activated form for assembly into protected actinonin **2**. Of these fragments, the suitably protected hydroxylamine **5** and amino acid-derived **3** units are readily accessible, whereas the α-pentylsuccinate fragment **4** is synthetically more challenging; this must be synthesized with unambiguous control over the stereochemistry.[9] Furthermore, it must be differentially protected and activated to facilitate regioselective couplings to the other fragments.



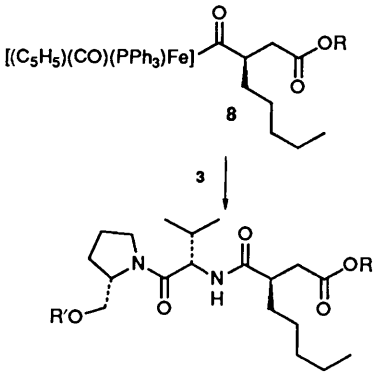
The asymmetric synthesis of the chiral succinyl fragment **4** may be achieved either by stereoselective alkylation of the enolate derived from a chiral heptanoyl equivalent **6** or from a chiral succinyl fragment **7**, both of which may be prepared from a chiral acetate enolate equivalent.

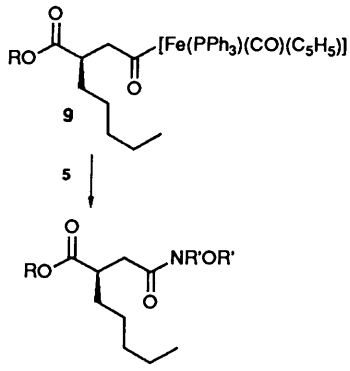


Aux = chiral auxiliary

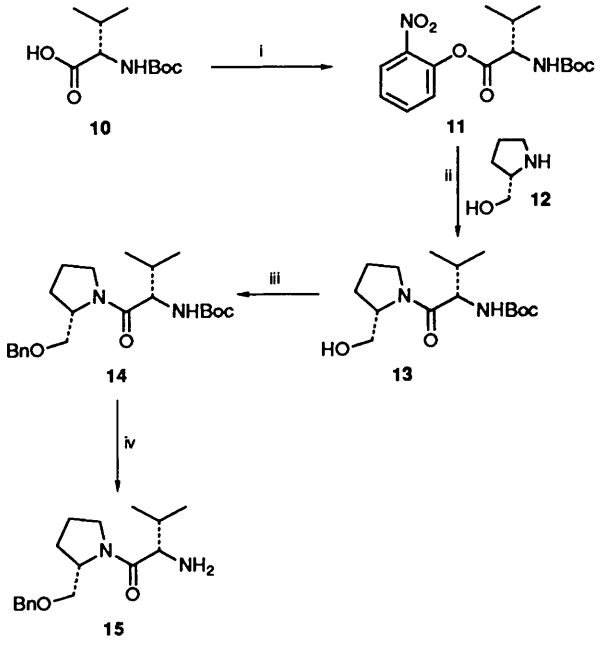
Both criteria required of the auxiliary – high asymmetric induction and differential protection of the product succinyl derivative – are fulfilled by the iron chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$.[10] The stereoselective formation of both succinyl derivatives **8** and **9** should therefore be possible. Oxidative decomplexation of compound **8** in the presence of amine **3** would give the required regioselective coupling as would decomplexation of compound **9** in the presence of the hydroxylamine **5**. In both cases the second coupling *via* deprotection and activation of the ester function should be straightforward. Furthermore, both enantiomers of the required chiral iron acetyl complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)(COMe)]$ are readily available.†

† Enantiomerically pure chiral iron acyls are available from Oxford Asymmetry, 57, Milton Park, Abingdon, Oxon, OX14 4RX, UK.



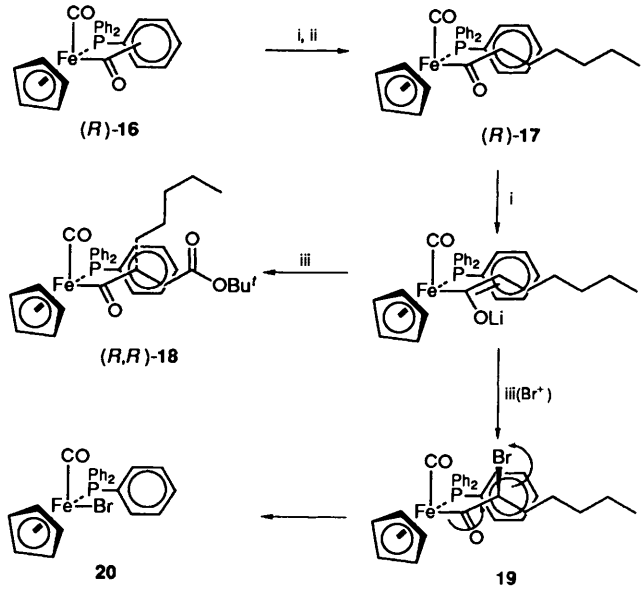


The *O*-benzyl-protected amino acid derived fragment **15** was prepared starting from *N*-Boc-L-valine **10** and L-prolinol **12**. *N*-Boc-L-valine **10** was transformed into the activated *o*-nitrophenol ester **11** by dicyclohexylcarbodiimide (DCC)-mediated coupling with *o*-nitrophenol. This compound reacted readily with L-prolinol **12** to give amide **13**. Benzylation of compound **13** with NaH/benzyl bromide proceeded smoothly, to give the diprotected dipeptide derivative **14** in 92% yield. Treatment of compound **14** with trifluoroacetic acid (TFA) then afforded *O*-benzyl-*N*-(L-valyl)-L-prolinol **15** quantitatively.



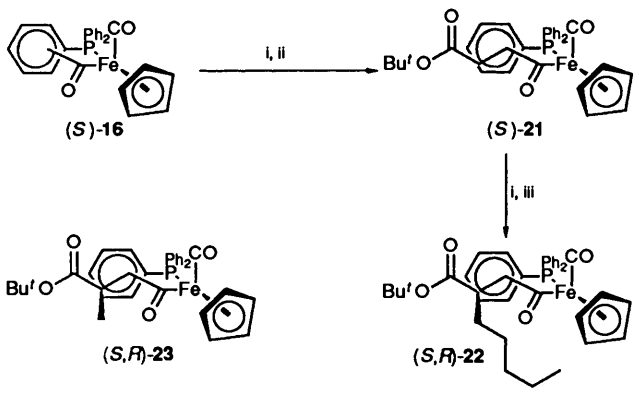
Reagents and yields: i, *o*-nitrophenol, DCC (88%); ii, **12** (85%); iii, NaH, BnBr (92%); iv, TFA (100%)

As described above, there are two approaches to the synthesis of the α-alkylsuccinate moiety **4**. In the first of these, homologation of the acetyl iron complex (*R*)-(−)-**16** was achieved by deprotonation at −78 °C with butyllithium followed by alkylation of the resulting enolate with 1-iodopentane, to provide the hexanoyl complex (*R*)-(−)-**17** in 96% yield. Deprotonation of compound **17** at −78 °C with butyllithium results in the formation of the *E*-enolate, in which the enolate oxygen lies *anti* to the carbon monoxide ligand of the iron in the reactive conformation.[11] In addition, the enolate lies in a plane roughly parallel to that of one of the phenyl groups of the PPh_3 ligand.[11] Thus alkylation of the enolate using *tert*-butyl bromoacetate afforded the (*R*,*R*)-α-pentylsuccinyl complex **18** with a diastereoisomeric excess (de) of greater than 98%, as determined by high-field ^1H NMR spectroscopy. A significant amount of starting material (19%) was also recovered, the formation of which can be accounted for by protonation of the enolate by an acidic proton from the electrophile. Separation of product from starting material was accomplished by column chromatography on silica gel. The yield of the pure, homochiral pentylsuccinyl complex (*R*,*R*)-(−)-**18** obtained in this manner was 46%. The incomplete mass balance may be explained by the probable formation of an α-bromacyl intermediate **19**, produced by bromination of the enolate by the electrophile. This species dissociates readily, giving the iron bromide **20** which was isolated, although it is somewhat unstable in solution.



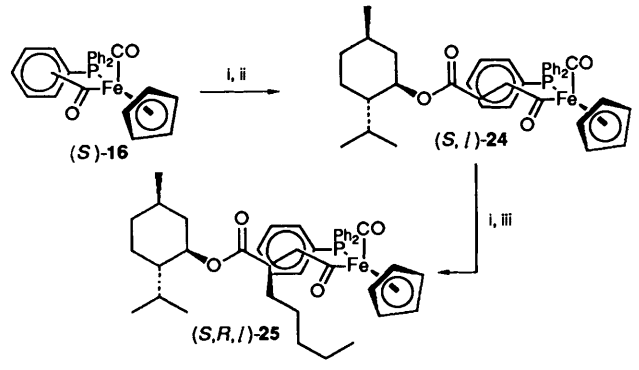
Reagents: i, BuLi; ii, $C_5H_{11}I$; iii, $BrCH_2CO_2Bu^t$

Employing the second strategy, the transformation of the acetyl iron complex (*S*)-(+)-**16** into the succinyl complex (*S*)-(+)-**21** was carried out in near quantitative yield by sequential deprotonation at −78 °C and alkylation using *tert*-butyl bromoacetate. Deprotonation of (*S*)-(+)-**21** with either butyllithium or lithium diisopropylamide (LDA) at −78 °C takes place completely regioselectively adjacent to the *tert*-butyl ester function, this being the more acidic site.[8] Alkylation at the β-position with respect to the iron acyl centre by using 1-iodopentane occurs with high stereoselectivity to produce the pentylsuccinyl complex (*S*,*R*)-(+)-**22** in 91% de according to the high-resolution ^1H NMR spectrum of the crude reaction mixture. Purification by column chromatography on alumina provided (*S*,*R*)-(+)-**22** as a single diastereoisomer (de > 99%) in 82% yield. The relative stereochemistry within this compound was assigned by direct analogy to the α-methylsuccinate (*S*,*R*)-(+)-**23**, which was prepared in the same fashion as (*S*,*R*)-(+)-**22** and whose configuration was determined unambiguously by X-ray crystallographic analysis.[12]



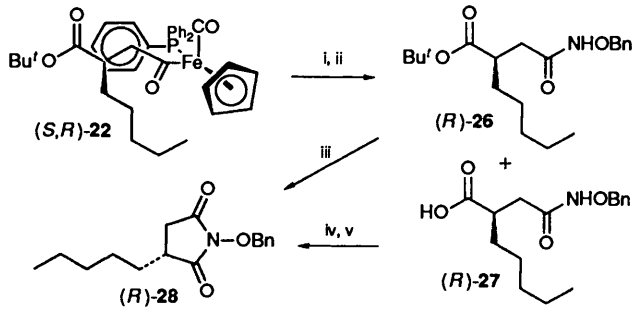
Reagents: i, BuLi; ii, $BrCH_2CO_2Bu^t$; iii, $C_5H_{11}I$

Our previous work has indicated that the nature of the alcohol part of the ester in iron succinyl complexes has a pronounced effect on the stereoselectivity of their alkylation reactions.[13] In fact, while the *tert*-butyl ester is the most readily available and least susceptible to side reactions, better selectivities were obtained when different alkoxy groups were present. The best results were obtained when an (*l*)-menthyl* ester was used. Although this alcohol unit is homochiral and should act as a chiral auxiliary in its own right, the influence of the chiral iron auxiliary at the other end of the succinyl backbone is completely overwhelming in determining the stereochemistry of the newly formed stereogenic centre.[13] Thus, in order to improve the diastereoselectivity of the pentylation of the succinate fragment of actinonin, the iron (*l*)-menthyl succinyl complex (*S*, *l*)-(+)-**24** was prepared in 61% yield by the reaction of the enolate of (*S*)-(+)-**16** with (*l*)-menthyl bromoacetate. Deprotonation of this compound with LDA and alkylation with 1-iodopentane furnished the complex (*S*, *R*, *l*)-(−)-**25** as a single diastereoisomer in 86% yield.



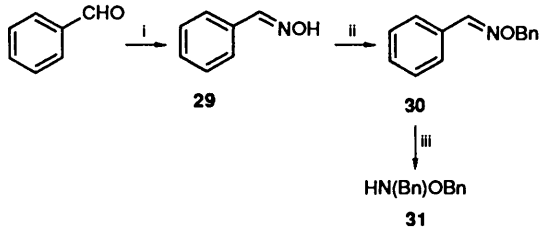
Reagents: i, BuLi; ii, *l*-menthyl bromoacetate; iii, $C_5H_{11}I$

The diprotected succinate equivalents may be selectively deprotected since oxidative conditions lead to the removal of only the iron unit, leaving the ester unaffected. When oxidative decomplexation of compounds bearing the iron chiral auxiliary are carried out in the presence of water, alcohols or amines, the organic products formed are acids, esters and amides, respectively.[11] Thus, treatment of the succinyl complex (*S*,*R*)-(+)-**22**, with bromine as the oxidant, in the presence of *O*-benzylhydroxylamine, produced a mixture of *tert*-butyl ester (*R*)-(+)-**26** and the corresponding acid (*R*)-(+)-**27**, which were readily separable by chromatography on silica gel. The formation of HBr during the decomplexation presumably brought about the *in situ* deprotection of the *tert*-butyl ester. Attempted removal of the *tert*-butyl protecting group from ester (*R*)-(+)-**26** by using TFA resulted in the formation of the succinimide derivative (*R*)-**28**, probably through an activated acid species which undergoes intramolecular attack from the nucleophilic nitrogen of the hydroxamate moiety. In an attempt to couple the acid (*R*)-(+)-**27** with the amine (*S*,*S*)-**15**, reaction of these two fragments with DCC and 1-hydroxybenzotriazole (HOBT) generated the succinimide derivative (*R*)-**28**.



Reagents: i, Br_2; ii, H_2NOBn; iii, TFA; iv, DCC, HOBT; v, **15**

In order to avoid these unwanted secondary reactions during deprotection of the *tert*-butyl ester and the subsequent coupling step, we required the dibenzylated compound **32**. This would be the product of decomplexation of (*S*,*R*)-(+)-**22** in the presence of *N*,*O*-dibenzylhydroxylamine **31**. This reagent was initially prepared by treatment of *O*-benzylhydroxylamine hydrochloride with potassium carbonate and benzyl bromide for 7 days (63% yield). Since significant amounts of *N*,*N*,*O*-tribenzylhydroxylamine were also formed (35%), a directed synthesis of compound **31** was undertaken. Reaction of benzaldehyde with hydroxylamine hydrochloride afforded the oxime **29**, which was *O*-benzylated with sodium hydride/benzyl bromide to give compound **30**, and this was then converted into the required compound **31** by reduction with sodium cyanoborohydride in methanol at pH < 3. The overall yield from benzaldehyde was 77%. While this route is two steps longer than the original synthesis, it is higher yielding, requires less time and is more cost efficient.

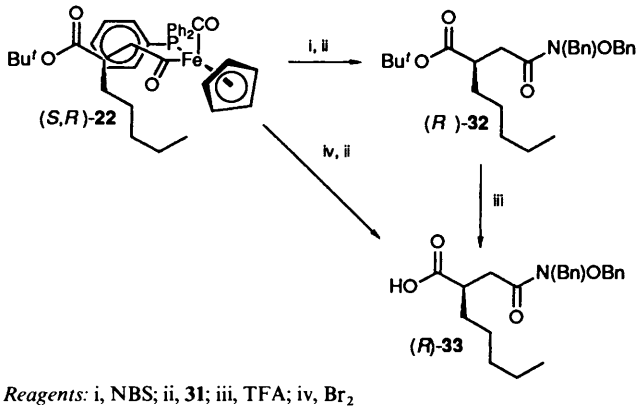


Reagents: i, H_2NOH·HCl; ii, NaH, $PhCH_2Br$; iii, $NaBH_3CN$

Oxidative decomplexation of the iron succinyl complex (*S*,*R*)-(+)-**22** by using *N*-bromosuccinimide (NBS) instead of bromine as the oxidant in the presence of reagent **31** afforded solely the homochiral *tert*-butyl derivative (*R*)-(+)-**32** in 94% yield. Treatment of this compound with TFA cleanly gave the free acid (*R*)-(+)-**33** in quantitative yield. Alternatively, decomplexation of (*S*,*R*)-(+)-**22** with bromine produced the acid (*R*)-(+)-**33** directly in 82% yield, the equivalent of HBr generated in the reaction being responsible for the cleavage of the *tert*-butyl ester.

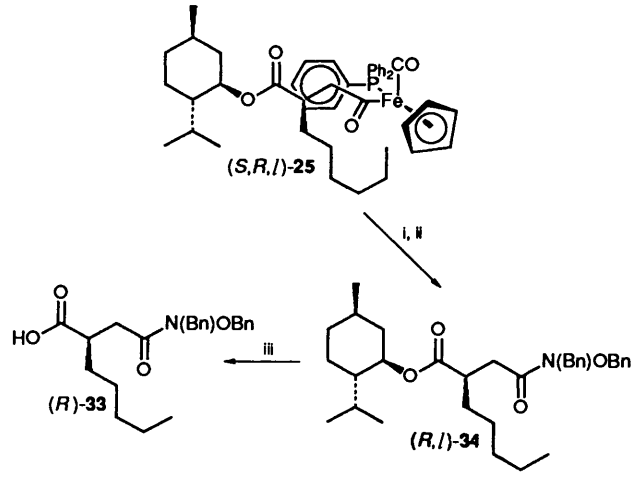
Decomplexation of the (*l*)-menthyl succinyl complex (*S*,*R*, *l*)-(−)-**25** also proceeded smoothly, to yield the protected hydroxaimic acid (*R*, *l*)-(−)-**34** (84%). However, the removal of the (*l*)-menthyl group proved to be problematic. Only starting material was recovered from treatment of ester (*R*,

* (*l*)-Menthol is (1*R*,2*S*,5*R*)-(−)-2-isopropyl-5-methylcyclohexan-1-ol. (*l*)-Menthyl is the radical formed by loss of the 1-hydroxy group.



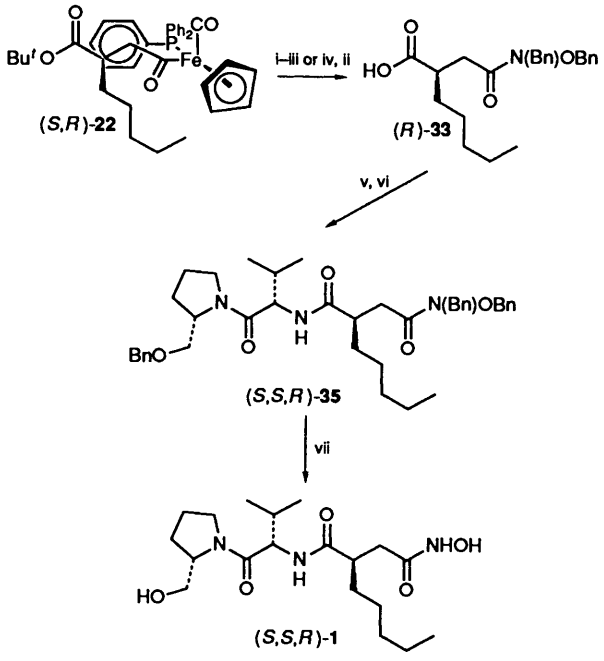
Reagents: i, NBS; ii, **31**; iii, TFA; iv, Br_2

l)-(−)-**34** with trimethylsilyl iodide,[14] or with the strongly nucleophilic phenylmethanethiolate,[15] or also with $(Bu_3Sn)_2O$[16] at room temperature, or in refluxing benzene, toluene or xylenes. Acid hydrolysis with aq. HCl/ethanol did not give any cleaved product and, furthermore, led to partial epimerisation of the starting material. Treatment with TFA at ambient temperature had no effect, whereas TFA at reflux caused slow decomposition. Under basic conditions (aq. KOH/ethanol) a good yield of (*l*)-menthol was isolated from the reaction, but no product resembling the desired acid (*R*)-(+)-**33** was observed. Treatment with KOH/dimethyl sulfoxide (DMSO) at 80 °C resulted in decomposition. Attempted transesterifications using HCl-saturated methanol and titanium(IV) isopropoxide[17] in ethanol also failed. $LiAlH_4$ reduced both the hydroxamic acid and ester groups. Acid (*R*)-(+)-**33** was eventually obtained in 26% yield by the reaction of ester (*R,l*)-(−)-**34** in refluxing $(Bu_3Sn)_2O$ (270 °C) for 7 days: No starting material was recovered from this reaction.



Reagents and conditions: i, NBS; ii, **31**; iii, $(Bu_3Sn)_2O$, heat

The next step was the coupling of the acid (*R*)-(+)-**33** with the peptide fragment (*S,S*)-**15** to form (*S,S,R*)-(−)-tribenzylactinonin **35**. For this, the mixed-anhydride method, using ethyl chloroformate and triethylamine, was selected.[18] Despite the mildness of this method, some epimerisation was observed, so a modified coupling procedure using isobutyl chloroformate and *N*-methylmorpholine was employed.[19] In this manner the target compound (*S,S,R*)-(−)-**35** was obtained in 83% yield. Catalytic hydrogenation over palladium hydroxide (20% on C) (Pearlman's catalyst) under hydrogen (2 atm) for 4 hours at 26 °C removed all three benzyl protecting groups, including the more stable *N*-benzyl group, to provide (*S,S,R*)-(−)-actinonin **1** in 89% yield. This deprotection is very temperature dependent, running to completion only after 15 h at 12 °C and under a pressure of 5 atm.



Reagents and conditions: i, NBS; ii, **31**; iii, TFA; iv, Br_2; v, $ClCO_2Bu^i$, *N*-methylmorpholine; vi, **15**; vii, $Pd(OH)_2/C$, H_2, 4 h, 26 °C

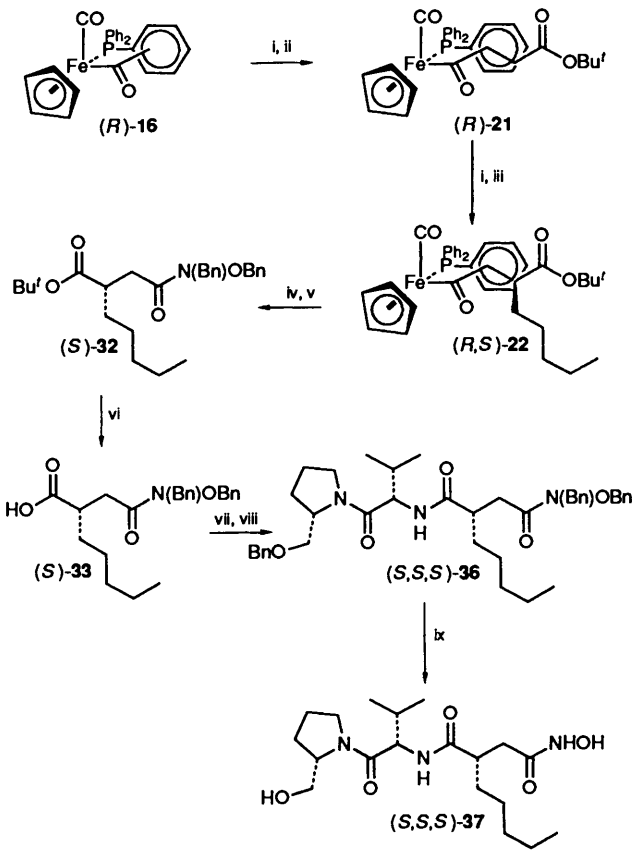
The total synthesis of pure, homochiral (*S,S,R*)-(−)-actinonin **1** was thus achieved *via* the procedure described above in an overall yield of 41% starting from the chiral iron acetyl complex (*S*)-(+)-[$(\eta^5$-$C_5H_5)Fe(CO)(PPh_3)$(COMe)] **16**. The product was identical in all respects with an authentic sample* including m.p., mixed m.p., high-field ^1H NMR and mixed ^1H NMR spectra and specific rotation.

Starting from the chiral iron acetyl complex (*R*)-(−)-[$(\eta^5$-$C_5H_5)Fe(CO)(PPh_3)$(COMe)] **16** the above sequence of reactions, employing the *tert*-butyl iron succinyl complexes (*R*)-(−)-**21** and (*R,S*)-(−)-**22**, provided diastereoisomerically pure (*S,S,S*)-(−)-*epi*-actinonin **37** in 43% overall yield. The key alkylation reaction to give (*R,S*)-(−)-**22** proceeded, as before, with high selectivity (de 91%), the minor diastereoisomer being removed by column chromatography on silica.

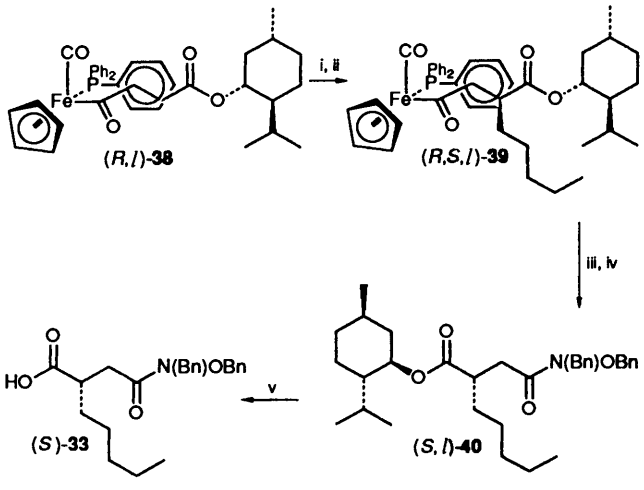
The synthesis of *epi*-actinonin **37** was also carried out using the iron (*l*)-menthyl succinyl complex (*R,l*)-(−)-**38**, which was alkylated to give complex (*R,S,l*)-(−)-**39** as a single diastereoisomer. Not only are the selectivities of the alkylations of the (*l*)-menthyl esters superior to those of the *tert*-butyl esters, but the diastereoisomeric iron (*l*)-menthyl succinyl complexes (*S,l*)-(+)-**24** and (*R,l*)-(−)-**38** could be prepared as a 1:1 mixture from racemic complex **16** and then separated by column chromatography, thereby eliminating the need to start from homochiral compound **16**. Decomplexation of compound (*R,S,l*)-(−)-**39** by using NBS in the presence of compound **31** gave the protected hydroxamic acid (*S,l*)-(−)-**40** in 90% yield. Again, the great resistance of the (*l*)-menthyl ester towards cleavage to the acid (*S*)-(+)-**33** dictated the use of drastic conditions and the yield (19%) was consequently poor.

For completeness, the minor diastereoisomers (*S,S*)-(+)-**41** and (*R,R*)-(−)-**42**, obtained from the alkylation of complexes (*S*)-(+)-**21** and (*R*)-(−)-**21**, were decomplexed by using NBS in the presence of BnONHBn **31** to give the esters (*R*)-(+)-**32** and (*S*)-(−)-**32** respectively.

* We thank Professor W. D. Ollis for the generous gift of an authentic sample of (−)-actinonin.



Reagents and conditions: i, BuLi; ii, $BrCH_2CO_2Bu^t$; iii, $C_5H_{11}I$; iv, NBS; v, **31**; vi, TFA; vii, $ClCO_2Bu^i$, *N*-methylmorphine; viii, **15**, ix, $Pd(OH)_2/C$, H_2, 15 h, 12 °C

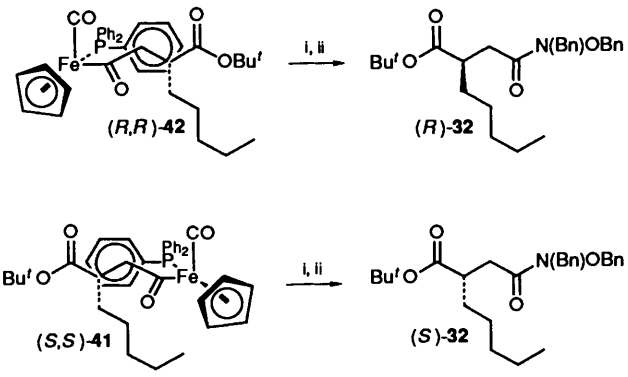


Reagents and conditions: i, LDA; ii, $C_5H_{11}I$; iii, NBS; iv, **31**; v, $(Bu_3Sn)_2O$, heat

Conclusions.—The total synthesis of (*S,S,R*)-(−)-actinonin **1** and its diastereoisomer (*S,S,S*)-(−)-*epi*-actinonin **37** in 41 and 43% overall yield from (*S*)-(+)- and (*R*)-(−)-[η^5-C_5H_5)Fe(CO)(PPh_3)(COMe)], respectively, are described. The procedure should be general for the synthesis of succinate-based protease inhibitors, of which the title compounds are but two examples.

Experimental

General.—All reactions and purifications involving organometallic compounds were carried out under an atmosphere of



Reagents: i, NBS; ii, **31**

nitrogen using vacuum-line and Schlenk-tube techniques[20] and all solvents for organometallic reactions were deoxygenated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Ether refers to diethyl ether and light petroleum refers to that fraction boiling in the range 40–60 °C. Butyllithium was used as a 1.4 or 1.6 mol dm^{-3} solution in hexane. 1-Iodopentane was dried over 4 Å molecular sieves. All other reagents were used as received. Flash chromatography was performed on silica (43–60 mm) and, for organometallic complexes, under a positive nitrogen pressure with deoxygenated solvents. Organic layers were dried using anhydrous magnesium sulfate.

^1H NMR spectra were recorded on a Bruker WM-300 spectrometer operating at 300.13 MHz using, unless otherwise stated, $CDCl_3$ as solvent and referenced to residual $CHCl_3$ with chemical shifts being reported as δ_H(ppm) from tetramethylsilane. ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer operating at 125.77 MHz using, unless otherwise stated, $CDCl_3$ as solvent and internal reference and chemical shifts are reported as δ_C(ppm) from tetramethylsilane. ^{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_P(ppm) from an external reference of triethyl phosphite in D_2O. *J*-Values are reported in Hz. IR spectra were obtained for chloroform solutions in 1 mm cells on a Perkin-Elmer 297 instrument calibrated against polystyrene (1601 cm^{-1}) or by using a Perkin-Elmer 1750 Infrared Fourier Transform Spectrometer. 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. Values for $[\alpha]_D$ are in 10^{-1} cm^2 g^{-1}. Elemental analyses were performed by the Dyson Perrins Laboratory Analytical Service. M.p.s were measured using a Kofler hot-stage apparatus and are uncorrected. Those of organometallic complexes were measured in sealed, nitrogen-filled capillaries.

N-*Boc*-L-*valine* o-*Nitrophenyl Ester* **11**.—To a solution of *N*-Boc-L-valine **10** (0.68 g, 3.1 mmol) and *o*-nitrophenol (0.78 g, 5.6 mmol) in pyridine (3 cm^3) was added DCC (0.65 g, 3.1 mmol). After the mixture had been stirred for 10 min, dicyclohexylurea precipitated out as a white solid. The mixture was stirred for 1 h and then filtered through Celite to provide a viscous residue, which was taken up in ether and refiltered. The solution was then acidified with 10% aq. citric acid and washed successively with aq. sodium hydrogen carbonate, water and brine. After drying and removal of solvents under reduced pressure, the residue was chromatographed on silica gel [ether–light petroleum (1:6), then ether] (R_f 0.7, Et_2O) to provide a pale yellow oil, which was crystallised from hexanes to give pure compound (*S*)-**11** as prisms (0.98 g, 92%), m.p. 56–57 °C; $[\alpha]_D^{20}$ −47.1 (*c* 0.15, $CHCl_3$) (Found: C, 56.8; H, 6.8. $C_{16}H_{22}N_2O_6$

requires C, 56.80; H, 6.55%); ν_{max}($CHCl_3$)/cm^{-1} 3351 (NH), 1774 (C=O, ester) and 1709 (C=O, Boc); δ_H 8.07 (1 H, dd, J_o 8.2, J_m 1.6, ArH *ortho* to NO_2), 7.66 (1 H, td, J_o 7.8, J_m 1.7, ArH *para* to NO_2), 7.41 (1 H, td, J_o 7.9, J_m 1.3, ArH *para* to O), 7.28 (1 H, d, J_o 7.4, ArH *ortho* to O), 5.06 (1 H, d, *J* 8.8, NH), 4.52 (1 H, dd, *J* 9.1 and 4.4, NHC*H*), 2.50–2.40 (1 H, m, C*H*Me_2), 1.48 (9 H, s, CMe_3), 1.11 (3 H, d, *J* 6.9, CH*Me*Me) and 1.04 (3 H, d, *J* 6.9, CHMe*Me*); δ_C 169.82 (s, C=O, ester), 155.61 (br s, C=O, Boc), 143.56 and 141.93 (s, Ar*C*-O, Ar*C*-N), 134.40 (d, ArC, *ortho* to O), 126.65, 125.48 and 124.97 (d, ArC), 79.95 (s, O*C*Me_3), 58.86 (br d, *C*HNH), 30.35 (d, *C*HMe_2), 28.17 (q, C*Me*$_3$), 19.29, (q, CH*Me*Me) and 17.16 (q, CHMe*Me*); *m*/*z* 338 (M^+), 138 and 57.

N-(N-*Boc*-L-*valyl*)-L-*prolinol* **13**.—To a solution of L-prolinol **12** (0.2 g, 2 mmol) and triethylamine (0.5 cm^3) in THF (30 cm^3) was added a solution ester of (*S*)-(−)-**11** (0.7 g, 2.05 mmol) in THF (5 cm^3) and the resulting deep yellow solution was stirred for 1 h. The reaction mixture was then concentrated and the residue was taken up in ether and washed successively with HCl (2 mol dm^{-3}), water, aq. sodium hydrogen carbonate, water and brine. After drying and removal of solvents, the residue was chromatographed on silica [gradient: ether–light petroleum (3:7 to 9:1)] [R_f 0.2, Et_2O–light petroleum (1:1)] to give pure *amide* (*S*,*S*)-(−)-**13** as an oil (0.51 g, 85%), $[\alpha]_D^{25}$ −29.8 (*c* 0.42, $CHCl_3$) (Found: C, 60.1; H, 9.45. $C_{15}H_{28}N_2O_4$ requires C, 59.96; H, 9.40%); ν_{max}($CHCl_3$)/cm^{-1} 3340br (OH), 1701 (C=O, Boc) and 1619 (C=O, amide); δ_H 5.25 (1 H, br m, NH), 4.68 (1 H, br s, OH), 4.35–4.21 (2 H, m, C*H*CH_2O and C*H*NH), 3.86–3.78 (1 H, m, NC*H*H′), 3.72–3.38 (3 H, m, CHCH_2O and NCH*H*′), 2.11–1.81 (4 H, m, $NCH_2CH_2CH_2$), 1.65–1.54 (1 H, m, C*H*Me_2), 1.43 (9 H, s, CMe_3), 0.97 (3 H, d, *J* 6.8, CH*Me*Me) and 0.92 (3 H, d, *J* 6.8, CHMe*Me*); δ_C 172.90 (2, C=O, amide), 155.71 (s, C=O, Boc), 79.28 (s, O*C*Me_3), 65.85 (t, CH_2OH), 60.58 and 57.06 (d, *C*HNCO*C*HNH), 47.86 (t, NCH_2), 31.26 (d, *C*HMe_2), 28.14 (q, C*Me*$_3$), 27.57 and 24.20 (t, $NCH_2CH_2CH_2$) and 19.11 and 17.34 (q, CH*Me*$_2$); the following peaks were observed for a minor amide rotamer (ratio ~4:1): δ_C 170.99 (s, C=O, amide), 156.12 (s, C=O, Boc), 79.59 (t, O*C*Me_3), 63.98 (t, CH_2OH), 59.45 and 57.06 (d, *C*HNCO*C*HNH), 45.32 (t, NCH_2), 32.10 (d, *C*HMe_2), 28.14 (q, C*Me*$_3$), 28.36 and 21.46 (t, $NCH_2CH_2CH_2$) and 18.89 and 18.04 (q, CH*Me*$_2$); *m*/*z* 301 (M^+ + 1), 57.

O-*Benzyl*-N-(N-*Boc*-L-*valyl*)-L-*prolinol* **14**.—A solution of the alcohol (*S*,*S*)-(−)-**13** (0.81 g, 2.7 mmol), sodium hydride (0.14 g, 3.2 mmol) and benzyl bromide (0.69 g, 4.1 mmol) in THF (20 cm^3) was stirred at room temperature for 36 h. The solvent was removed and the residue was taken up in ether (100 cm^3). The reaction mixture was then concentrated and the residue was taken up in ether and washed successively with HCl (2 mol dm^{-3}), water, aq. sodium hydrogen carbonate, water and brine. After drying and removal of solvents, the residue was chromatographed on silica [gradient: ether–light petroleum 3:7 to 9:1)] [R_f 0.6, ether–light petroleum (1:1)] to give compound (S,S)-(−)-**14** (0.96 g, 92%) as an oil, $[\alpha]_D^{20}$ −51.9 (*c* 1.0, $CHCl_3$) (Found: C, 67.7; H, 9.0. $C_{22}H_{34}N_2O_4$ requires C, 67.66; H, 8.78%); ν_{max}($CHCl_3$)/cm^{-1} 3299 (NH), 1713 (C=O, Boc) and 1636 (C=O, amide); δ_H 7.38–7.23 (5 H, m, ArH), 5.30–5.25 (1 H, br m, NH), 4.52 (1 H, d, *J* 12.0, C*H*H′Ph), 4.47 (1 H, d, *J* 12.0, CH*H*′Ph), 4.41–4.28 (1 H, m, C*H*CH_2O), 4.28 (1 H, dd, *J* 9.2 and 6.1, C*H*NH), 3.72–3.38 (4 H, m, CHCH_2O and NCH_2), 2.10–1.84 (5 H, m, $NCH_2CH_2CH_2$ and C*H*Me_2), 1.44 (9 H, s, CMe_3), 0.96 (3 H, d, *J* 6.8, CH*Me*Me) and 0.90 (3 H, d, *J* 6.7, CHMe*Me*); δ_C 170.79 (s, C=O, amide), 155.73 (s, C=O, Boc), 138.35 (s, ArC_{ipso}), 128.12 (d, ArC_{ortho}), 127.30 (d, ArC_{para}), 127.23 (d, ArC_{meta}), 79.06 (s, O*C*Me_3), 73.04 and 70.08 (t, *C*H_2OCH_2), 56.85 and 56.51 (d, *C*HNCO*C*HN), 47.42 (t, NCH_2), 31.44 (d, *C*HMe_2), 28.20 (q, OC*Me*$_3$), 27.47 and 24.34 (t, $NCH_2CH_2CH_2$) and 19.22 and 17.26 (q, CH*Me*$_2$); the following peaks were observed for a minor amide rotamer (ratio 5:1): δ_C 155.32 (s, C=O, Boc), 138.25 (s, ArC_{ipso}), 127.54 and 127.44 (d, ArC), 78.98 (s, O*C*Me_3), 73.26 and 70.97 (t, *C*H_2OCH_2), 45.46 (t, NCH_2), 32.52 (d, *C*HMe_2), 28.51 and 21.48 (t, $NCH_2CH_2CH_2$) and 19.01 and 17.80 (q, CH*Me*$_2$); *m*/*z* 391 (M^+ + 1).

O-*Benzyl*-N-(L-*valyl*)-L-*prolinol* **15**.—To a stirred solution of compound (*S*,*S*)-(−)-**14** (0.82 g, 2.7 mmol) in dichloromethane (5 cm^3) at room temperature was added TFA (3 cm^3). The residue was taken up in ether and washed with aq. $NaHCO_3$, dried and concentrated to give pure O-*benzyl*-N-(L-*valyl*)-L-*prolinol* **15** as an oil (1.1 g, 100%), $[\alpha]_D^{20}$ −42.4 (*c* 1.0, $CHCl_3$) (Found: C, 70.4; H, 9.1, $C_{17}H_{26}N_2O_2$ requires C, 70.31; H, 9.02%); ν_{max}($CHCl_3$)/cm^{-1} 3390br (NH_2) and 1646 (C=O); δ_H 7.37–7.28 (5 H, m, ArH), 4.58–4.43 (2 H, m, CH_2Ph), 4.43–4.33 (1 H, m, C*H*CH_2O), 3.67–3.30 (5 H, m, CHCH_2O, C*H*NH and NCH_2), 2.12–1.77 (5 H, m, $NCH_2CH_2CH_2$ and C*H*Me_2), 1.61 (2 H, br s, NH_2), 0.98 (3 H, d, *J* 6.8, CH*Me*Me) and 0.92 (3 H, d, *J* 6.8, CHMe*Me*); δ_C 173.22 (s, C=O), 138.24 (s, ArC_{ipso}), 127.93 (d, ArC_{ortho}), 127.06 (d, ArC_{para}, ArC_{meta}), 72.86 and 70.03 (t, *C*H_2OCH_2), 57.98 and 56.39 (d, *C*HNCO*C*HN), 46.96 (t, NCH_2), 31.85 (d, *C*HMe_2), 26.95 and 24.18 (t, $NCH_2CH_2CH_2$) and 19.42 and 16.65 (q, CH*Me*$_2$); the following peaks were observed for a minor amide rotamer (ratio ~2:1): δ_C 174.57 (s, C=O), 137.41 (s, ArC_{ipso}), 128.17 (d, ArC_{ortho}), 127.56 (d, ArC_{para}), 127.36 (d, ArC_{meta}), 73.13 and 71.21 (t, *C*H_2OCH_2), 58.13 and 56.31 (d, *C*HNCO*C*HN), 44.86 (t, NCH_2), 32.55 (d, *C*HMe_2), 28.27 and 21.33 (t, $NCH_2CH_2CH_2$) and 19.28 and 17.85 (q, CH*Me*$_2$); *m*/*z* 291 (M^+ + 1), 72.

(R)-(−)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*CO*[CH_2]$_5$*Me* **17**.—To a stirred solution of acetyl complex (*R*)-(−)-**16** (1.0 g, 2.2 mmol) in THF (20 cm^3) at −78 °C was added BuLi (2.6 mmol) and the colour of the solution became deep red. The mixture was stirred for 20 min and 1-iodopentane (0.54 cm^3, 4.4 mmol) was added. The reaction mixture was allowed slowly to reach room temperature during 5 h, quenched with MeOH (1 cm^3) and concentrated. The residue was filtered over a plug of grade V alumina using dichloromethane and the solvent was once more evaporated. Chromatography on alumina with ether–light petroleum (gradient: 1:1 to pure ether) [R_f 0.7, ether–light petroleum (2:1)] afforded *compound* (R)-(−)-**17** as a bright orange oil (1.11 g, 96%), $[\alpha]_D^{21}$ −173 (*c* 0.083, benzene) (Found: C, 71.1; H, 6.4. $C_{31}H_{33}FeO_2P$ requires C, 71.00; H, 6.34%); ν_{max}($CHCl_3$)/cm^{-1} 1910 (C≡O) and 1602 (C=O); δ_H 7.57–7.46 (6 H, m, ArH_{ortho}), 7.42–7.32 (9 H, m, ArH_{meta}, ArH_{para}), 4.42 (5 H, d, J_{PH} 1.2, C_5H_5), 2.81–2.41 (1 H, m, COC*H*H′), 2.60–2.50 (1 H, m, COCH*H*′), 1.28–0.96 (8 H, m, [CH_2]$_4$) and 0.84 (3 H, t, *J* 7.2, Me); δ_C 274.16 (d, J_{PC} 23.2, C=O), 221.44 (d, J_{PC} 31.1, C≡O), 136.72 (d, J_{PC} 44.1, ArC_{ipso}), 133.51 (dd, J_{PC} 10.0, ArC_{ortho}), 129.77 (d, ArC_{para}), 128.14 (dd, J_{PC} 9.1, ArC_{meta}), 85.25 (d, C_5H_5), 66.41 (td, J_{PC} 5.7, $COCH_2$), 31.65, 28.73, 24.98 and 22.41 (t, [CH_2]$_4$) and 13.96 (q, CH_2Me); *m*/*z* 525 (M^+ + 1).

(R, R)-(−)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*(C_5H_{11})CH_2-CO_2Bu^t **18**.—To a solution of complex (*R*)-(−)-**17** (0.27 g, 0.51 mmol) in THF (20 cm^3) at −78 °C was added BuLi (0.62 mmol) and, after the mixture was stirred for 30 min, *tert*-butyl bromoacetate (0.15 cm^3, 0.92 mmol) was added. After reaction at −78 °C for 1 h, the mixture was allowed to warm slowly to room temperature and was then quenched with methanol (1 cm^3). The solvent was removed and the residue was subjected to column chromatography on activated alumina with ether–light petroleum (1:3) [R_f 0.7, ether–light petroleum (2:1)] to obtain all the orange coloured bands. The solvent was removed, and

the new residue was chromatographed on a column of silica with ether–light petroleum (1:15) to separate two bands. The first, minor band gave starting material (*R*)-(−)-**17** (0.051 g, 19% recovery), while the second, major band provided pure α-pentylsuccinyl complex (*R,R*)-(−)-**18** (0.15 g, 46%) as a bright yellow oil, $[\alpha]_D^{24}$ −34.4 (*c* 0.08, benzene) (Found: C, 69.8; H, 6.9. $C_{37}H_{43}FeO_4P$ requires C, 69.59; H, 6.79%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1913 (C≡O), 1723 (C=O, ester) and 1610 (C=O, iron); δ_H 7.60–7.50 (6 H, m, ArH_{ortho}), 7.42–7.32 (9 H, m, ArH_{meta}, ArH_{para}), 4.47 (5 H, d, J_{PH} 1.3, C_5H_5), 3.16–3.08 (1 H, m, COCH), 2.68 (1 H, dd, *J* 15.2 and 5.6, $CHH'CO_2Bu^t$), 2.12 (1 H, dd, *J* 15.2 and 6.8, $CHH'CO_2Bu^t$), 1.58–0.97 (8 H, m, $[CH_2]_4$), 1.45 (9 H, s, CMe_3) and 0.82 (3 H, d, *J* 7.2, Me); *m/z* 639 (M^+ + 1).

(S)-(+)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*$_2$*CO*$_2$*Bu*^{t} **21**.[13]—To a solution of complex (*S*)-(+)-**16** (0.914 g, 2.01 mmol) in THF (20 cm^3) at −78 °C was added BuLi (2.05 mmol) and, after being stirred for 30 min, was treated with *tert*-butyl bromoacetate (0.63 cm^3, 3.9 mmol). After reaction at −78 °C for 5 min, the mixture was quenched with methanol (1 cm^3) and the solvent was removed. The residue was subjected to column chromatography on activated alumina with ether–light petroleum (1:3) [R_f 0.7, ether–light petroleum (1:1)] to give compound (*S*)-(+)-**21** as bright orange microcrystals (1.11 g, 97%), $[\alpha]_D^{23}$ + 190 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1914 (C≡O), 1723 (C=O, ester) and 1605 (C=O, iron); δ_H 7.56–7.47 (6 H, m, ArH_{ortho}), 7.43–7.32 (9 H, m, ArH_{meta}, ArH_{para}), 4.46 (5 H, d, J_{PH} 1.2, C_5H_5), 3.23 (1 H, td, *J* 17.4 and 7.6, $FeCOCHH'$), 2.72 (1 H, ddd, *J* 17.4, 7.0 and 5.8, $FeCOCHH'$), 2.13 (1 H, td, *J* 16.1 and 7.5, $CHH'CO_2Bu^t$), 1.70 (1 H, ddd, *J* 16.1, 7.4 and 5.5, $CHH'CO_2Bu^t$) and 1.41 (9 H, s, CMe_3); *m/z* 569 (M^+ + 1).

(R)-(−)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*$_2$*CO*$_2$*Bu*^{t} **21**.[13]—The above experiment was repeated using (*R*)-(−)-**16** (1.50 g, 3.29 mmol) for the preparation of compound (*R*)-(−)-**21** (1.82 g, 97%) $[\alpha]_D^{23}$ −190 (*c* 1.0, $CHCl_3$). The spectroscopic data for this compound were identical with those of (*S*)-(+)-**21**.

(S,R)-(+)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*(C_5H_{11})-*CO*$_2$*Bu*^{t} **22**.—To a solution of complex (*R*)-(−)-**21** (1.93 g, 3.40 mmol) in THF (40 cm^3) at −78 °C was added LDA [prepared from diisopropylamine (1.5 cm^3) and butyllithium (3.6 mmol)]. After the mixture had been stirred for 30 min, 1-iodopentane (0.60 cm^3, 4.5 mmol) was added to the orange-brown enolate and the reaction mixture was allowed to warm to room temperature during 4 h. After a quench with methanol (1 cm^3) and removal of the solvents, the crude residue was chromatographed on a column of silica [ether–light petroleum (3:17)] [R_f 0.7, ether–light petroleum (1:1)]. The first, faint band was collected to give the *minor diastereoisomer* (S,S)-(+)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*(C_5H_{11})*CO*$_2$*Bu*^{t} **41** as an orange solid (81 mg, 4%), m.p. 42–44 °C; $[\alpha]_D^{23}$ + 109.6 (*c* 0.5, $CHCl_3$) (Found: C, 69.8; H, 7.0. $C_{37}H_{43}FeO_4P$ requires C, 69.59; H, 6.79%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1914 (C≡O), 1711 (C=O, ester) and 1600 (C=O, iron); δ_H 7.55–7.46 (6 H, m, ArH_{ortho}), 7.40–7.32 (9 H, m, ArH_{meta}, ArH_{para}), 4.44 (5 H, d, J_{PH} 1.1, C_5H_5), 3.34 (1 H, dd, *J* 17.5 and 8.7, $COCHH'$), 2.46 (1 H, dd, *J* 17.6 and 4.7, $COCHH'$), 2.31–2.22 (1 H, m, $CHCO_2Bu^t$), 1.43 (9 H, s, CMe_3), 1.35–1.05 (8 H, m, $[CH_2]_4$) and 0.86 (3 H, t, *J* 7.1, CH_2Me); δ_C 273.65 (d, J_{PC} 23.2, C=O, iron), 220.54 (d, J_{PC} 31.2, C≡O), 175.72 (s, C=O, ester), 136.57 (d, J_{PC} 42.6, ArC_{ipso}), 133.38 (dd, J_{PC} 9.0, ArC_{ortho}), 129.62 (d, ArC_{para}), 127.98 (dd, J_{PC} 9.1, ArC_{meta}), 85.33 (d, C_5H_5), 79.21 (s, $OCMe_3$), 67.18 (t, $FeCOCH_2$), 42.21 (d, CH_2CHCO), 31.82, 31.63, 26.74 and 22.43 (t, $[CH_2]_4$), 28.14 (q, $OCMe_3$) and 13.96 (q, CH_2Me); δ_P 72.52; *m/z* 72.52; *m/z* 639 (M^+ + 1).

Further elution afforded the *pentylsuccinyl complex* (S,R)-(+)-**22** as orange microcrystals (1.78 g, 82%), $[\alpha]_D^{21}$ + 28.7 (*c* 0.08, benzene) (Found: C, 69.7; H, 7.0); $\nu_{max}(CHCl_3)/cm^{-1}$ 1914 (C≡O), 1723 (C=O, ester) and 1605 (C=O, iron); δ_H 7.49–7.41 (6 H, m, ArH_{ortho}), 7.40–7.32 (9 H, m, ArH_{meta}, ArH_{para}), 4.41 (5 H, d, J_{PH} 1.1, C_5H_5), 3.06 (1 H, dd, *J* 17.1 and 6.7, $COCHH'$), 2.79 (1 H, dd, *J* 17.1 and 6.7, $COCHH'$), 2.39–2.35 (1 H, m, $CHCO_2Bu^t$), 1.36 (9 H, s, CMe_3), 1.27–1.15 (8 H, m, $[CH_2]_4$) and 0.86 (3 H, t, *J* 6.8 CH_2Me); δ_C 272.72 (d, J_{PC} 23.2, C=O, iron), 220.22 (d, J_{PC} 30.9, C≡O), 175.32 (s, C=O, ester), 136.40 (d, J_{PC} 42.8, ArC_{ipso}), 133.28 (dd, J_{PC} 7.8, ArC_{ortho}), 129.60 (d, ArC_{para}), 127.99 (dd, J_{PC}, 8.0, ArC_{meta}), 85.16 (d, C_5H_5), 79.12 (s, $OCMe_3$), 67.34 (t, $FeCOCH_2$), 42.46 (d, CH_2CHCO), 32.07, 31.74, 26.99 and 22.46 (t, $[CH_2]_4$), 28.07 (q, $OCMe_3$) and 13.94 (q, CH_2Me); δ_P 72.90; *m/z* 639 (M^+ + 1).

(R, S)-(−)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*(C_5H_{11})-*CO*$_2$*Bu*^{t} **22**.—The procedure described above was repeated on succinoyl complex (*R*)-(−)-**21** (2.10 g, 3.69 mmol), using diisopropylamine (1.5 cm^3), BuLi (3.9 mmol) and adding 1-iodopentane (0.97 cm^3, 7.4 mmol). Work-up and chromatography as above provided (R,R)-(−)-(η^5-C_5H_5)*Fe*(*CO*)-(*PPh*$_3$)*COCH*$_2$*CH*(C_5H_{11})*CO*$_2$*Bu*^{t} **42** (0.085 g, 4%) as an orange solid, m.p. 42–44 °C; $[\alpha]_D^{23}$ −109.8 (*c* 0.5, $CHCl_3$) (Found: C, 69.8; H, 7.0%); the spectroscopic properties of this compound were identical with those of (*S,S*)-(+)-(η^5-C_5H_5)-Fe(CO)(PPh_3)$COCH_2CH(C_5H_{11})CO_2Bu^t$ described above.

Further elution afforded *pentylsuccinate complex* (*R, S*)-(−)-**22** as orange microcrystals (1.88 g, 80%), $[\alpha]_D^{24}$ −28.4 (*c* 0.08, benzene) (Found: C, 69.3; H, 6.6%). The spectroscopic data for this compound were identical with those of compound (*S,R*)-(+)-**22**.

(S,l)-(+)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*$_2$*CO*$_2$*Menthyl* **24**.—To a solution of (*S*)-(+)-**16** (1.5 g, 3.3 mmol) in THF (40 cm^3) at −78 °C was added BuLi (4.0 mmol) and, after the mixture had been stirred for 1 h, neat (*l*)-menthyl bromoacetate (1.5 g, 5.41 mmol) was added. After being stirred for 30 min at −78 °C, the reaction mixture was quenched with methanol (1 cm^3) and the solvent was removed. The residue was pre-adsorbed and chromatographed on silica [ether–light petroleum (1:2)] [R_f 0.3, ether–light petroleum (1:2)] to yield *complex* (S,l)-(+)-**24** as an orange solid (1.31 g, 61%), m.p. 55–58 °C; $[\alpha]_D^{23}$ +36.6 (*c* 0.50, $CHCl_3$) (Found: C, 70.2; H, 6.8. $C_{38}H_{43}FeO_4P$ requires C, 70.16; H, 6.66%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1917 (C≡O), 1715 (C=O, ester) and 1604 (C=O, iron); δ_H 7.52–7.42 (6 H, m, ArH_{ortho}), 7.40–7.33 (9 H, m, ArH_{meta} and ArH_{para}), 4.89 (1 H, td, *J* 10.9 and 4.3, OCH), 4.45 (5 H, d, *J* 1.1, C_5H_5), 3.23 (1 H, td, *J* 17.5 and 7.6, $COCHH'$), 2.76 (1 H, ddd, *J* 17.5, 7.7 and 5.4, $COCHH'$), 2.24 (1 H, td, *J* 16.0 and 7.5, $CHH'CO_2Bu^t$), 1.98–1.92 (1 H, m, menthyl), 1.83 (1 H, quint-d, *J* 7.0 and 2.6, menthyl), 1.73 (1 H, ddd, *J* 16.0, 7.8 and 5.3, $CHH'CO_2Bu^t$), 1.70–0.83 (7 H, m, menthyl), 0.90 (3 H, d, *J* 6.7, $CHMeMe$), 0.88 (3 H, d, *J* 7.2, $CHMeMe$) and 0.73 (3 H, d, *J* 7.0, $CHMe$); δ_C 272.67 (d, J_{PC} 26.4, C=O, iron), 220.39 (d, J_{PC} 31.4, C≡O), 173.44 (s, C=O, ester), 136.50 (d, J_{PC} 42.9, ArC_{ipso}), 133.37 (dd, J_{PC} 9.3, ArC_{ortho}), 129.70 (d, ArC_{para}), 128.04 (dd, J_{PC} 9.4, ArC_{meta}), 85.23 (d, C_5H_5), 73.76 (d, OCH), 59.57 (t, $FeCOCH_2$), 47.19 (d, OCHCH), 41.02 (t, $OCHCH_2$), 34.42 (t, CH_2CH_2CHMe), 31.41 (d, CH_2CHMe), 30.15 (t, $CH_2CO_2Bu^t$), 26.32 (d, $CHMe_2$), 23.72 (t, CH_2CH_2CHMe), 21.98 (q, CH_2CHMe), 20.72 (q, $CHMeMe$) and 16.48 (q, $CHMeMe$); δ_P 72.56; *m/z* 651 (M^+ + 1).

Further elution afforded (*S*)-(+)-**16** (0.375 g, 25%).

(R,l)-(−)-(η^5-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*$_2$*CO*$_2$*Menthyl* **38**.—The above procedure was repeated using (*R*)-(−)-**16** (1.5 g, 3.3 mmol), BuLi (4 mmol) and (*l*)-menthyl bromoacetate (1.5 g, 5.41 mmol). Work-up and chromatography [R_f 0.35 ether–light petroleum (1:2)] afforded *complex* (R, l)-(−)-**38** as

an orange solid (1.27 g, 59%), m.p. 116–117 °C; $[\alpha]_D^{23}$ −107.4 (*c* 0.50, $CHCl_3$) (Found: C, 70.3; H, 6.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1917 (C≡O), 1715 (C=O, ester) and 1604 (C=O, iron); δ_H 7.52–7.42 (6 H, m, ArH_{ortho}), 7.40–7.32 (9 H, m, ArH_{meta} and ArH_{para}), 4.89 (1 H, td, *J* 10.9 and 4.4, OCH), 4.44 (5 H, d, *J* 1.2, C_5H_5), 3.26 (1 H, td, *J* 17.5 and 7.6, COCH*H*'), 2.77 (1 H, ddd, *J* 17.5, 7.4 and 5.4, COCH*H*'), 2.23 (1 H, td, *J* 15.9 and 7.5, C*H*H'CO_2Bu^t), 1.96–1.98 (2 H, m, menthyl), 1.73 (1 H, ddd, *J* 15.9, 7.5 and 5.3, CH*H*'CO_2Bu^t), 1.72–0.84 (7 H, m, menthyl), 0.91 (3 H, d, *J* 7.0, CH*Me*Me), 0.90 (3 H, d, *J* 6.6, CHMe*Me*) and 0.76 (3 H, d, *J* 6.9, CH*Me*); δ_C 272.36 (d, J_{PC} 22.6, C=O, iron), 220.45 (d, J_{PC} 31.4, C≡O), 173.42 (s, C=O, ester), 136.53 (d, J_{PC} 43.0, ArC_{ipso}), 133.37 (dd, J_{PC} 9.1, ArC_{ortho}), 129.69 (d, ArC_{para}), 128.03 (dd, J_{PC} 9.2, ArC_{meta}), 85.23 (d, C_5H_5), 73.73 (d, OCH), 59.59 (t, FeCO*C*H_2), 47.23 (d, OCH*C*H), 41.01 (t, OCH*C*H_2), 34.43 (t, CH_2*C*H-$_2$CHMe), 31.41 (d, CH_2*C*HMe), 30.23 (t, *C*$H_2CO_2Bu^t$), 26.25 (d, *C*HMe_2), 23.72 (t, *C*H_2CH_2CHMe), 21.99 (q, CH_2CH*Me*), 20.76 (q, CH*Me*Me) and 16.54 (q, CHMe*Me*); δ_P 72.63; *m*/*z* 651 (M^+ + 1).

Further elution afforded (*R*)-(−)-**16** (0.341 g, 23%).

(S,l)-(+)-(η⁵-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*$_2$*CO*$_2$-*Menthyl* **24** *and* (R, l)-(−)-(η⁵- C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*$_2$-*CO*$_2$-*Menthyl* **38**.—The above procedure was repeated using (*RS*)-**16** (10.4 g, 22.9 mmol), BuLi (25.1 mmol) and (*l*)-menthyl bromoacetate (7.62 g, 27.5 mmol). Work-up and chromatography [ether–light petroleum (1:2)] afforded a 1:1 mixture (8.52 g, 57%) of complexes (*S*, *l*)-(+)-**24** and (*R*, *l*)-(−)-**38** as an orange solid, and then (*RS*)-**16** (2.25 g, 22%). Further chromatography [ether–light petroleum (3:17)] gave, first, complex (*R*, *l*)-(−)-**38** (4.19 g, 28%) (R_f 0.15) and then complex (*S*, *l*)-(+)-**24** (4.1 g, 27%) (R_f 0.11) as orange solids. The physical and spectroscopic properties of these compounds were identical with those of the complexes derived from homochiral substrate **16**.

(S, R, l)-(−)-(η⁵-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*(C_5H_{11})-*CO*$_2$*Menthyl* **25**.—To a solution of complex (*S*,*l*)-(+)-**24** (1.1 g, 1.69 mmol) in THF (40 cm^3) at −78 °C was added LDA (1.8 mmol). After 1 h, 1-iodopentane (0.27 cm^3, 2.1 mmol) was added to the orange-brown enolate and the reaction was stirred at −78 °C for 3 h and at −50 °C for 3 h. The reaction was quenched with methanol (1 cm^3), the solvents were removed, and the crude residue was chromatographed on a column of silica [ether–light petroleum (1:3)] [R_f 0.45, ether–light petroleum (1:2)]. The first coloured band provided the *pentylsuccinyl complex* (S, R, l)-(−)-**25** as orange microcrystals (1.05 g, 86%), m.p. 52–54 °C; $[\alpha]_D^{23}$ −25.8 (*c* 0.50, $CHCl_3$); (Found: C, 71.5; H, 7.4. $C_{43}H_{53}FeO_4P$ requires C, 71.66; H, 7.41%); ν_{max}(CH-Cl_3)/cm^{-1} 1918 (C≡O), 1714 (C=O, ester) and 1603 (C=O, iron); δ_H 7.49–7.41 (6 H, m, ArH_{ortho}), 7.40–7.32 (9 H, m, ArH_{meta}, ArH_{para}), 4.56 (1 H, td *J* 10.8 and 4.3, OCH), 4.39 (5 H, d, J_{PH} 1.1, C_5H_5), 3.17 (1 H, dd, *J* 17.1 and 7.4, FeCOCH*H*'), 2.88 (1 H, dd, *J* 17.2 and 5.7, FeCOCH*H*'), 2.47–2.41 (1 H, m, C*H*CO_2menthyl), 1.94–1.88 (2 H, m, menthyl), 1.68–0.81 (15 H, m, menthyl and $[CH_2]_4$), 0.90–0.84 (9 H, m, CH*Me*) and CH_2*Me*) and 0.65 (3 H, d, *J* 6.9, CH*Me*); δ_C 271.62 (d, J_{PC} 20.1, C=O, iron), 220.30 (d, J_{PC} 31.4, C≡O), 175.46 (s, C=O, ester), 136.65 (d, J_{PC} 43.0, ArC_{ipso}), 133.40 (dd, J_{PC} 9.6, ArC_{ortho}), 129.64 (d, ArC_{para}), 128.03 (dd, J_{PC} 8.8, ArC_{meta}), 85.19 (d, C_5H_5), 73.52 (d, OCH), 67.20 (t, FeCO*C*H_2), 47.23 (d, OCH*C*H), 42.12 (d, CH_2*C*HCO), 40.98 (t, OCH*C*H_2), 34.50 (t, CH_2*C*H_2CHMe), 32.12, 31.87, 27.07 and 22.50 (t, $[CH_2]_4$), 31.45 (d, CH_2*C*HMe), 25.90 (d, *C*HMe_2), 23.43 (t, *C*H_2CH_2CHMe), 21.98 (q, CH_2CH*Me*), 20.90 (q, CH*Me*Me), 16.10 (q, CHMe*Me*) and 13.90 (q, CH_2*Me*); δ_P 72.99; *m*/*z* 721 (M^+ + 1).

Further elution afforded (*S*, *l*)-(+)-**24** (0.128 g, 12%).

(R, S, l)-(−)-(η⁵-C_5H_5)*Fe*(*CO*)(*PPh*$_3$)*COCH*$_2$*CH*(C_5H_{11})-*CO*$_2$*Menthyl* **39**.—The above procedure was repeated using (*R*, *l*)-(−)-**38** (2.2 g, 3.38 mmol), LDA (3.8 mmol) and 1-iodopentane (0.6 cm^3, 5 mmol). Work-up and chromatography [ether–light petroleum (1:3)] [R_f 0.45, ether–light petroleum (1:2)] afforded 2.20 g *complex* (R, S, l)-(−)-**39** (2.2 g, 90%) as an orange solid, m.p. 48–51 °C; $[\alpha]_D^{23}$ −20.4 (*c* 0.50, $CHCl_3$) (Found: C, 71.85; H, 7.5%): $\nu_{max}(CHCl_3)/cm^{-1}$ 1918 (C≡O), 1714 (C=O, ester) and 1603 (C=O, iron); δ_H 7.50–7.41 (6 H, m, ArH_{ortho}), 7.40–7.32 (9 H, m, ArH_{meta}, ArH_{para}), 4.50 1 H, td, *J* 10.9 and 4.2, OCH), 4.40 (5 H, d, J_{PH} 1.2, C_5H_5), 3.17 (1 H, dd, *J* 17.4 and 6.6, FeCOC*H*H'), 2.88 (1 H, dd, *J* 17.4 and 6.3, FeCOCH*H*'), 2.44–2.39 (1 H, m, C*H*CO_2menthyl), 1.90 (1 H, quint-d, *J* 7.0 and 2.7, menthyl), 1.80–1.73 (1 H, m, menthyl), 1.69–0.83 (15 H, m, menthyl and $[CH_2]_4$), 0.89–0.86 (9 H, m, C*H*Me_2 and CH_2*Me*) and 0.71 (3 H, d, *J* 7.0, CH*Me*); δ_C 271.80 (d, J_{PC} 22.6, C=O, iron), 220.25 (d, J_{PC} 33.7, C≡O), 175.45 (s, C=O, ester), 136.58 (d, J_{PC} 42.4, ArC_{ipso}), 133.38 (dd, J_{PC} 9.2, ArC_{ortho}), 129.62 (d, ArC_{para}), 128.02 (dd, J_{PC} 9.1, ArC_{meta}), 85.19 (d, C_5H_5), 73.53 (d, OCH), 67.53 (t, FeCO*C*H_2), 47.13 (d, OCH*C*H), 42.09 (d, CH_2*C*HCO), 40.70 (t, OCH*C*H_2), 34.58 (t, CH_2*C*H_2CHMe), 31.95, 31.80, 27.15 and 22.48 (t, $[CH_2]_4$), 31.38 (d, CH_2*C*HMe), 26.11 (d, *C*HMe_2), 23.54 (t, *C*H_2CH_2-CHMe), 21.99 (q, CH_2CH*Me*), 20.73 (q, CH*Me*Me), 16.19 (q, CHMe*Me*) and 13.85 (q, CH_2*Me*); δ_P 72.90; *m*/*z* 721 (M^+ + 1).

Further elution afforded starting material (0.185 g, 8%).

(R)-(+)-tert-*Butyl* 2-(N-*Benzyloxycarbamoylmethyl*)*heptanoate* **26** *and* (R)-(+)-2-(N-*Benzyloxycarbamoylmethyl*)*heptanoic Acid* **27**.—To a stirred solution of the succinyl complex (*S*,*R*)-(+)-**22** (0.45 g, 0.75 mmol) in dichloromethane (15 cm^3) at −40 °C was added dropwise bromine (81 mm^3, 1.4 mmol). The resulting green solution was stirred for 20 min and a solution of *O*-benzylhydroxylamine (0.41 g, 1.9 mmol) in dichloromethane (10 cm^3) was added. After 30 min at −40 °C, the reaction mixture was allowed to reach 20 °C and was stirred for a further 1.5 h. The solvent was then evaporated off and the green residue was subjected to column chromatography on flash silica [ether–light petroleum (3:7), then ether] [R_f **26** 0.6, ether–light petroleum (1:2); R_f **27** 0.3, ether–light petroleum (2:1)] to give, first, the tert-*butyl* ester (R)-(+)-**26** as an oil (0.18 g, 68%), $[\alpha]_D^{23}$ +5.5 (*c* 0.18, $CHCl_3$) (Found: C, 68.7; H, 9.0. $C_{20}H_{31}NO_4$ requires C, 68.76; H, 8.94%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 (C=O, ester) and 1660 (C=O, hydroxamate); δ_H 8.57 (1 H, br s, NH), 7.43–7.30 (5 H, m, ArH), 4.88 (2 H, m, OCH_2), 2.86–2.74 (1 H, m, C*H*CO_2Bu^t), 2.41–2.08 (2 H, m, C*H*$_2$CHCO$_2$Bu^t), 1.45 (9 H, s, CMe_3), 1.35–1.22 (8 H, m, $[CH_2]_4$), 0.88 (3 H, br t, CH_2*Me*); *m*/*z* 350 (M^+ + 1); and then the *α-pentylsuccinic acid* **27** (0.050 g, 23%) as an oil, $[\alpha]_D^{23}$ +6.1 (*c* 0.21, $CHCl_3$) (Found: C, 65.8; H, 7.7. $C_{16}H_{23}NO_4$ requires C, 65.51; H, 7.90%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1708 (C=O, acid) and 1662 (C=O, hydroxamate); δ_H 8.92 (1 H, br s, NH), 7.37–7.28 (5 H, m, ArH), 4.88 (2 H, m, OCH_2), 2.88–2.74 (1 H, m, C*H*CO_2H), 2.47–2.25 (2 H, m, C*H*$_2$CHCO$_2$H), 1.68–1.22 (8 H, m, $[CH_2]_4$) and 0.87 (3 H, br t, CH_2*Me*); *m*/*z* 294 (M^+ + 1).

N,O-*Dibenzylhydroxylamine* **31**.—To a solution of hydroxylamine hydrochloride (8.17 g, 118 mmol) and sodium acetate (8.23 g, 100 mmol) in water (150 cm^3) was added freshly distilled benzaldehyde (7.28 g, 68.6 mmol). The mixture was stirred for 3 h and extracted with two portions of ether (100 cm^3). The united organic layers were washed with water, then dried, and the solvent was removed, to give benzaldehyde oxime **29** (8.24 g, 99%) as an oil, δ_H 8.18 (1 H, s, CH=N), 7.62–7.56 (2 H, m, ArH_{ortho}) and 7.43–7.38 (3 H, m, ArH_{meta}, ArH_{para}).

Sodium hydride (3.16 g of 60%; 1.90 g, 79.0 mmol) was washed with two portions of THF and then slurried with THF (25 cm^3). To this was added a solution of oxime **29** (8.2 g, 67.8

mmol) in THF (15 cm^3) followed by a catalytic amount of tetrabutylammonium iodide. After being stirred overnight and then evaporated the mixture gave a residue, which was slurried with dichloromethane and filtered through a plug of Celite. Removal of the solvent afforded (14.2 g, 99%) *O*-benzyl benzaldehyde oxime **30** as a faintly yellow oil, δ_H 8.16 (1 H, s, CH=N), 7.62–7.57 (2 H, m, ArH_{ortho} CH=N), 7.44–7.31 (8 H, m, ArH) and 5.24 (2 H, s, CH_2).

To a solution of sodium cyanoborohydride (4.0 g, 63.6 mmol) in methanol (100 cm^3) were added compound **30** (4.22 g, 20 mmol) and 5 drops of methyl orange solution. The pH was kept at < 3 (pink colouration of the indicator) by the dropwise addition of conc. HCl solution. After 30 min, the pink colour no longer faded and the reaction mixture was stirred overnight. After removal of the solvent, the residue was slurried with water (150 cm^3) and the pH was adjusted to 9 (using pH paper) by the addition of 20% aq. potassium hydroxide. Extraction with dichloromethane (2 × 100 cm^3), followed by drying and removal of the solvent gave a yellow oil, which was chromatographed on silica with ether–light petroleum (1:4) [R_f 0.5, ether–light petroleum (1:4)]. The yield of pure *N,O*-dibenzylhydroxylamine **31** was 3.38 g (79%), δ_H 7.43–7.28 (10 H, m, ArH), 4.68 (2 H, s, OCH_2) and 4.08 (2 H, s, NCH_2).

(R)-(+)-tert-*Butyl* 2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)*heptanoate* **32** [*from complex* (S,R)-(+)-**22**].—To a solution of the succinyl complex (*S,R*)-(+)-**22** (0.74 g, 1.2 mmol) in dichloromethane (40 cm^3) at −40 °C was added a solution of NBS (0.23 g, 1.3 mmol) and, after this mixture had been stirred for 30 min, a solution of *N*, *O*-dibenzylhydroxylamine **31** (0.29 g, 1.4 mmol) was added. After being stirred for 30 min, the mixture was allowed to reach 20 °C and was stirred for a further 2 h. The solvent was evaporated off and the green residue was subjected to column chromatography on flash silica [ether–light petroleum (1:2)] [R_f 0.6, ether–light petroleum (1:1)]. All fractions containing product were united and rechromatographed using ether–light petroleum (1:3) to give pure ester (*R*)-(+)-**32** (0.48 g, 94%); $[\alpha]_D^{20}$ +6.3 (*c* 2.3, $CHCl_3$) (Found: C, 73.7; H, 8.6. $C_{27}H_{37}NO_4$ requires C, 73.77; H, 8.48%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1724 (C=O, ester) and 1669 (C=O, hydroxamate); δ_H 7.38–7.28 (10 H, m, ArH), 4.83–4.74 (4 H, m, OCH_2 and NCH_2), 2.91–2.82 (2 H, m, C*H*H′C*H*CO_2Bu^t), 2.48–2.41 (1 H, m, CH*H*′$CHCO_2Bu^t$), 1.46 (9 H, s, CMe_3), 1.31–1.23 (8 H, m, $[CH_2]_4$) and 0.89 (3 H, br t, Me); δ_C 174.70 (s, C=O, ester), 173.54 (s, C=O, hydroxamate), 136.59 and 134.62 (s, ArC_{ipso}), 129.15, 128.54, 128.50 and 128.40, (d, ArC_{ortho}, ArC_{meta}), 128.76 and 127.50 (d, ArC_{para}), 80.01 (s, $OCMe_3$), 77.06 (t, OCH_2), 50.39 (br t, NCH_2), 41.55 (d, *C*HCO), 34.54 (t, *C*H_2CO), 32.16, 31.56, 26.51 and 22.37 (t, $[CH_2]_4$), 28.02 (q, $OCMe_3$) and 13.87 (q, CH_2Me); *m/z* 440 (M^+ + 1).

(R)-(+)-tert-*Butyl* 2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)*heptanoate* **32** [*from complex* (R,R)-(−)-**42**].—The succinyl complex (*R,R*)-(−)-**42** (50 mg, 0.078 mmol) was decomplexed by the procedure described above, using NBS (16 mg, 0.09 mmol) and *N,O*-dibenzylhydroxylamine **31** (21 mg, 0.099 mmol) to give pure compound (*R*)-(+)-**32** (29 mg, 85%). The product was identical in all respects with that obtained above.

(S)-(−)-tert-*Butyl* 2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)*heptanoate* **32** [*from complex* (R,S)-(−)-**22**.—The succinyl complex (*R,S*)-(−)-**22** (0.54 g, 0.84 mmol) was decomplexed by the procedure described above, using NBS (0.17 g, 0.93 mmol) and *N,O*-dibenzylhydroxylamine **31** (0.21 g, 1.00 mmol) to give pure *compound* (S)-(−)-**32** (0.35 g, 94%); $[\alpha]_D^{20}$ −6.8 (*c* 1.8, $CHCl_3$) (Found: C, 73.9; H, 8.5, $C_{27}H_{37}NO_4$ requires C, 73.77; H, 8.48%). The spectroscopic data for this compound were identical with those of (*R*)-(+)-**32**.

(S)-(−)-tert-*Butyl* 2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)*heptanoate* **32** [*from complex* (S,S)-(+)-**41**].—The succinyl complex (*S,S*)-(+)-**41** (50 mg, 0.078 mmol) was decomplexed by the procedure described above, using NBS (16 mg, 0.09 mmol) and *N,O*-dibenzylhydroxylamine **31** (21 mg, 0.099 mmol) to give pure compound (*S*)-(−)-**32** (31 mg, 90%). The product was identical in all respects with that obtained from (*R,S*)-(−)-**22**.

(R,l)-(−)-*Menthyl* 2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)*heptanoate* **34**.—The succinyl complex (*S,R,l*)-(−)-**25** (2.62 g, 3.64 mmol) was decomplexed by the procedure described above, using NBS (0.777, g, 4.37 mmol) and *N,O*-dibenzylhydroxylamine **31** (0.789 g, 3.70 mmol) to give pure *title compound* as an oil (1.60 g, 84%), $[\alpha]_D^{23}$ −14.4 (*c* 1.0, $CHCl_3$) (Found: C, 76.0; H, 9.1. $C_{33}H_{47}NO_4$ requires C, 75.97; H, 9.08%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (C=O, ester) and 1661 (C=O, hydroxamate); δ_H 7.39–7.28 (10 H, m, ArH), 4.85–4.74 (4 H, m, NCH_2 and OCH_2), 4.72 (1 H, td, *J* 10.8 and 4.3, OCH), 2.98–2.90 (2 H, m, C*H*H′C*H*CO_2menthyl), 2.53–2.42 (1 H, m, CH*H*′$CHCO_2$menthyl), 2.03–1.94 (2 H, m, menthyl), 1.71–0.87 (15 H, m, menthyl and $[CH_2]_4$), 0.93–0.89 (9 H, m, $CHMe_2$ and CH_2Me) and 0.78 (3 H, d, *J* 7.0, CH*Me*); δ_C 174.88 (s, C=O, ester), 173.31 (br s, C=O, hydroxamate), 136.66 and 134.65 (s, ArC_{ipso}), 129.16 (d, ArC_{ortho}), 128.79, 128.56 and 128.45 (d, ArC), 127.53 (d, ArC_{para}), 77.07 (t, OCH_2), 74.09 (d, OCH), 50.49 (br, t, NCH_2), 47.12 (d, OCH*C*H), 41.07 (d, *C*HCO), 40.85 (t, OCH*C*H_2), 34.44 and 34.36 (t, CH_2CH_2CHMe, CH_2CO), 32.16, 31.61, 26.56 and 22.37 (t, $[CH_2]_4$), 31.38 (d, CH_2CHMe), 26.02 (d, *C*HMe_2), 23.41 (t, CH_2CH_2CHMe), 21.97 (q, CH_2CHMe), 20.73 and 16.18 (q, $CHMe_2$) and 13.87 (q, CH_2Me); *m/z* 522 (M^+ + 1).

(S,l)-(−)-*Menthyl* 2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)*heptanoate* **40**.—The succinyl complex (*R, S, l*)-(−)-**39** (0.9 g, 1.25 mmol) was decomplexed by the procedure described above, using NBS (0.235 g, 1.32 mmol) and *N,O*-dibenzylhydroxylamine **31** (0.268 g, 1.26 mmol) to give pure *compound* (S,l)-(−)-**40** (0.584 g, 90%) as an oil, $[\alpha]_D^{23}$ −46.0 (*c* 1.0, $CHCl_3$) (Found: C, 75.95; H, 9.1. $C_{33}H_{47}NO_4$ requires C, 75.97; H, 9.08%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (C=O, ester) and 1661 (C=O, hydroxamate); δ_H 7.38–7.28 (10 H, m, ArH), 4.90–4.70 (4 H, m, NCH_2 and OCH_2), 4.68 (1 H, td, *J* 10.9 and 4.3, OCH), 2.96–2.86 (2 H, m, C*H*H′C*H*CO_2menthyl), 2.55–2.45 (1 H, m, CH*H*′$CHCO_2$menthyl), 2.07–2.00 (1 H, m, menthyl), 1.93 (1 H, quint-d, *J* 7.0 and 2.7, menthyl), 1.72–0.84 (15 H, m, menthyl and $[CH_2]_4$), 0.92–0.86 (9 H, m, $CHMe_2$ and CH_2Me), 0.75 (3 H, d, *J* 7.0, CH*Me*); δ_C 175.05 (s, C=O, ester), 173.36 (br, s, C=O, hydroxamate), 136.60 and 134.64 (s, ArC_{ipso}), 129.13, 128.78, 128.56 and 128.44 (d, ArC), 127.54 (d, ArC_{para}), 77.06 (t, OCH_2), 74.27 (d, OCH), 50.50 (br, t, NCH_2), 46.99 (d, OCH*C*H), 41.09 (d, *C*HCO), 40.70 (t, OCH*C*H_2), 34.58 and 34.35 (t, CH_2CH_2CHMe, CH_2CO), 32.00, 31.65, 26.58 and 22.40 (t, $[CH_2]_4$), 31.40 (d, CH_2CHMe), 25.93 (d, *C*HMe_2), 23.17 (t, CH_2CH_2CHMe), 21.94 (q, CH_2CHMe), 20.80 and 15.90 (q, $CHMe_2$) and 13.85 (q, CH_2Me); *m/z* 522 (M^+ + 1).

(R)-(+)-2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)-*heptanoic Acid* **33** [*from complex* (S,R)-(+)-**22**].—To a stirred solution of the succinyl complex (*S,R*)-(+)-**22** (0.58 g, 0.91 mmol) in dichloromethane (20 cm^3) at −40 °C was added dropwise bromine (58 mm^3, 0.11 mmol). The resulting green solution was stirred for 20 min and a solution of *N,O*-dibenzylhydroxylamine **31** (0.29 g 1.4 mmol) in dichloromethane (5 cm^3) was then added. After being stirred for 30 min, the mixture was allowed to reach 20 °C and was stirred for a further 1.5 h. The solvent was evaporated off and the green residue was subjected to column chromatography on flash silica [ether–light

petroleum (7:3), then ether] [R_f 0.3 in ether–light petroleum (7:3)] to yield the *product* (R)-(+)-**33** as an oil (0.29 g, 82%), $[\alpha]_D^{25}$ +5.2 (*c* 1.3, $CHCl_3$) (Found: C, 72.5; H, 7.8. $C_{23}H_{29}NO_4$ requires C, 72.37; H, 7.62%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1708 (C=O, acid) and 1660 (C=O, hydroxamate); δ_H 7.39–7.27 (10 H, m, ArH), 5.02–4.61 (4 H, m, OCH_2 and NCH_2), 2.97–2.81 (2 H, m, $CHH'CHCO_2H$), 2.54–2.43 (1 H, m, $CHH'CHCO_2H$), 1.71–1.22 (8 H, m, $[CH_2]_4$) and 0.89 (3 H, br t, CH_2Me); δ_C 180.76 (s, C=O, acid), 173.55 (br, s, C=O, hydroxamate), 136.27 and 134.48 (s, ArC_{ipso}), 129.25, 128.64, 128.60 and 128.51 (d, ArC_{ortho}, ArC_{meta}), 128.92 and 127.65 (ArC_{para}), 77.06 (t, OCH_2), 50.38 (br, t, NCH_2), 40.69 (d, *C*HCO), 34.15 (t, *C*HCO), 31.76, 31.57, 26.59 and 22.35 (t, $[CH_2]_4$) and 13.91 (q, CH*Me*); the following peaks were observed for a minor amide rotamer: δ_C 177.69 (s, C=O, acid), 176.47 (br s, C=O, hydroxamate), 136.48 (s, ArC_{ipso}), 129.19 and 128.78 (d, ArC), 50.11 (br t, NCH_2), 37.32 (d, *C*HCO), 35.53 (t, CH_2CO), 31.66 and 26.37 (t, two of $[CH_2]_4$ and 13.86 (q, CH_2Me); *m/z* 384 (M^+ + 1).

(R)-(+)-2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)-*heptanoic Acid* **33** [*from ester* (R)-(+)-**32**].—To a stirred solution of ester (*R*)-(+)-**32** (0.129 g, 2.94 mmol) in dichloromethane (1 cm^3) at 10 °C was added TFA (1.5 cm^3). The mixture was stirred for 1 h at room temperature and the solvent was evaporated off. The residue was purified by chromatography on silica gel [gradient: ether–light petroleum (1:2) to ether] (R_f 0.8, Et_2O) to provide 0.113 g pure acid (*R*)-(+)-**33** (0.113 g, 100%) as an oil, which was identical in all respects with the sample obtained from the above experiment.

(S)-(−)-2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)-*heptanoic Acid* **33** [*from ester* (S)-(−)-**32**].—The above reaction was repeated on the *tert*-butyl ester (*S*)-(−)-**32** (0.15 g, 0.34 mmol) in dichloromethane (1 cm^3), with TFA (1 cm^3) to provide, after chromatography, the pure *acid* (S)-(−)-**33** (0.13 g, 100%) as an oil, $[\alpha]_D^{25}$ −5.2 (*c* 1.3, $CHCl_3$) (Found: C, 72.5; H, 7.7. $C_{23}H_{29}NO_4$ requires C, 72.37; H, 7.62%). The spectrographic data for this compound were identical with those of (*R*)-(+)-**33**.

(R)-(+)-2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)-*heptanoic Acid* **33** [*from ester* (R, 1)-(−)-**34**].—The ester (*R*, *l*)-(−)-**34** (0.101 g, 0.194 mmol) was heated with bis(tributyltin) oxide (1 cm^3) at 270 °C for 7 days. After cooling, the reaction mixture was stirred with 6 mol dm^{-3} aq. HCl, for 15 min, extracted with ether and the residue was chromatographed on silica [slow gradient: light petroleum to ether–light petroleum (2:1)] to afford pure acid (*R*)-(+)-**33** (0.019 g, 26%) as an oil, which was identical in all respects with the sample obtained from the reaction of ester (*R*)-(+)-**32** and TFA (*vide supra*).

(S)-(−)-2-(N-*Benzyl*-N-*benzyloxycarbamoylmethyl*)-*heptanoic Acid* **33** [*from ester* (S,l)-(−)-**40**].—The ester (*S*,*l*)-(−)-**40** (0.088 g, 0.169 mmol) was heated with bis(tributyltin) oxide (1 cm^3) at 270 °C for 7 days. After cooling, the reaction mixture was stirred with 6 mol dm^{-3} aq. HCl for 15 min, extracted with ether, and the residue was chromatographed on silica [slow gradient: light petroleum to ether–light petroleum (2:1)] to afford pure acid (*S*)-(−)-**33** as an oil (0.012 g, 19%), which was identical in all respects with the sample obtained from the reaction of ester (*S*)-(−)-**32** and TFA (*vide supra*).

(S,S,R)-(−)-*Tribenzylactinonin* **35**.—To a solution of the acid (*R*)-(+)-**33** (62 mg, 0.16 mmol) in THF (5 cm^3) at 0 °C were added *N*-methylmorpholine (20 mg, 0.19 mmol) and isobutyl chloroformate (24 mg, 0.18 mmol). After the mixture had been stirred for 4 min, a solution of amine (*S*,*S*)-(−)-**15** (65 mg, 0.23 mmol) in THF (3 cm^3) was added and the mixture was stirred for a further 15 min before being allowed to warm to room temperature, and was then stirred for another 1 h. The solvent was evaporated off and the residue was taken up in ether (40 cm^3) and washed successively with water, 0.5 mol dm^{-3} HCl, water, aq. sodium hydrogen carbonate, water and saturated aq. sodium chloride. The organic layer was dried and the solvent was evaporated off. The residue was chromatographed on silica [gradient: ether–light petroleum (1:5) to pure ether] (R_f 0.5, Et_2O) to provide pure (S,S,R)-(−)-*tribenzylactinonin* **35** as an oil (88 mg, 83%), $[\alpha]_D^{22}$ −43.4 (*c* 1.0, $CHCl_3$) (Found: C, 73.2; H, 8.3. $C_{40}H_{53}N_3O_5$ requires C, 73.25; H, 8.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3298 (NH) and 1625 (C=O); δ_H 7.37–7.25 (15 H, m, ArH), 6.54 (1 H, d, *J* 9.1, NH), 4.85–4.71 (4 H, m, CH_2NOCH_2), 4.63 (1 H, dd, *J* 9.1 and 6.8, *CH*NH), 4.53 (1 H, d, *J* 12.0, $CHOCHH'Ph$), 4.49 (1 H, d, *J* 12.3, $CHOCHH'Ph$), 4.35–4.31 (1 H, m, $NCHCH_2$), 3.75–3.39 (4 H, m, NCH_2CH_2 and $CHCH_2O$), 2.98 (1 H, dd, *J* 16.6 and 9.4, $COCHH'$), 2.80–2.74 (1 H, m, COCH), 2.47 (1 H, dd, *J* 16.8 and 4.1, $COCHH'$), 2.09–1.85 (4 H, m, $NCH_2CH_2CH_2$), 1.43–1.36 (1 H, m, $CHMe_2$), 1.36–1.22 (8 H, m, $[CH_2]_4$), 0.97–0.92 (6 H, m, $CHMe_2$) and 0.86 (3 H, br t, CH_2Me); the following signals for a minor amide rotamer (~7:1 ratio) were observed: δ_H 6.49 (1 H, d, *J* 9.1, NH) and 4.21–4.15 (1 H, m, $NCHCH_2$); δ_C 174.65 [s, *C*(O)NH], 173.45 (br s, C=O, hydroxamate), 170.33 (s, NHCH*C*O), 138.33 (s, ArC_{ipso} of $BnOCH_2$), 136.40 and 134.45 (s, ArC_{ipso}), 129.02, (d, ArC_{ortho}), 128.59 (d, ArC_{para}), 128.38 and 128.28, (d, ArC_{ortho}, ArC_{meta}), 128.10 (d, ArC_{ortho} of $BnOCH_2$), 127.37 (d, ArC_{para}), 127.26, (d, ArC_{para} of $BnOCH_2$), 127.21 (d, ArC_{meta} of $BnOCH_2$), 76.92 (t, CH_2ON), 73.02 and 70.03 (t, CH_2OCH_2), 56.50 and 55.41 [d, *C*HNC(O)*C*HNH], 50.32 (br t, NCH_2Ph), 47.47 (t, NCH_2CH_2), 42.26 (d, CH_2CHCO), 35.16 (t, CH_2CO), 32.41, 31.47, 26.69 and 22.22 (t, $[CH_2]_4$), 31.38 (d, $CHMe_2$), 27.19 and 24.30 (t, $NCH_2CH_2CH_2$), 19.23 and 17.53 (q, $CHMe_2$) and 13.71 (q, CH_2Me); the following peaks were observed for a minor amide rotamer (ratio ~5:1); 174.20 [s, *C*(O)NH], 138.13 (s, ArC_{ipso} of $BnOCH_2$), 73.23 and 70.90 (t, CH_2OCH_2), 56.76 and 55.25 [d, *C*HNC(O)*C*HNH], 45.49 (t, NCH_2CH_2), 32.48 (d, *C*HMe$_2$), 28.44 and 21.45 (t, $NCH_2CH_2CH_2$) and 19.00 and 18.00 (q, $CHMe_2$); *m/z* 656 (M^+ + 1).

(S,S,S)-(−)-*Tribenzyl*-epi-*actinonin* **36**.—The above procedure was applied to the acid (*S*)-(−)-**33** (68 mg, 0.18 mmol), *N*-methylmorpholine (22 mg, 0.21 mmol), isobutyl chloroformate (27 mg, 0.19 mmol) and amine (*S*,*S*)-(−)-**15** (72 mg, 0.25 mmol) to provide, after chromatography (R_t 0.4, Et_2O), (S,S,S)-(−)-*tribenzyl*-epi-*actinonin* **36** (109 mg, 94%), $[\alpha]_D^{23}$ −54.2 (*c* 0.8, $CHCl_3$) (Found: C, 73.3; H, 8.35. $C_{40}H_{53}N_3O_5$ requires C, 73.25; H, 8.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3298 (NH) and 1620 (C=O); δ_H 7.39–7.26 (15 H, m, ArH), 6.54 (1 H, d, *J* 8.6, NH), 4.86–4.41 (4 H, m, CH_2NOCH_2), 4.63 (1 H, dd, *J* 8.6 and 6.4, *CH*NH), 4.52 (1 H, d, *J* 12.0, $CHOCHH'Ph$), 4.48 (1 H, d, *J* 12.3, $CHOCHH'Ph$), 4.34–4.29 (1 H, m, $NCHCH_2$), 3.76–3.46 (4 H, m, NCH_2CH_2 and $CHCH_2O$), 2.88 (1 H, dd, *J* 16.1 and 8.2, $COCHH'$), 2.82–2.75 (1 H, m, COCH), 2.47 (1 H, dd, *J* 16.1 and 4.5, $COCHH'$), 2.06–1.80 (4 H, m, $NCH_2CH_2CH_2$), 1.69–1.64 (1 H, m, $CHMe_2$), 1.47–1.22 (8 H, m, $[CH_2]_4$), 0.96 (3 H, d, *J* 5.8, CH*Me*Me), 0.92 (3 H, d, *J* 6.8, CHMe*Me*) and 0.88 (3 H, t, *J* 6.8, CH_2Me); δ_C 174.93 [s, C(O)NH], 173.49 (br s, C=O, hydroxamate), 170.32 (s, NHCHCO), 138.45 (s, ArC_{ipso} of $BnOCH_2$), 136.49 and 134.57 (s, ArC_{ipso}), 129.11 (d, ArC_{ortho}), 128.69 (d, ArC_{para}), 128.47, 128.42 and 128.37 (d, ArC_{ortho}, ArC_{meta}), 128.18 (d, ArC_{ortho} of $BnOCH_2$), 127.43 (d, ArC_{para}), 127.36, (d, ArC_{para} of $BnOCH_2$), 127.30 (d, ArC_{meta} of $BnOCH_2$), 77.00 (t, CH_2ON), 73.12 and 70.20 (t, CH_2OCH_2), 56.61 and 55.72 [d, *C*HNC(O)*C*HNH], 50.41 (br t, NCH_2Ph), 47.55 (t, NCH_2CH_2), 42.23 (d, CH_2CHCO), 35.16 (t,

CH_2CO), 32.48, 31.62, 26.93 and 22.36 (t, $[CH_2]_4$), 31.37 (d, $CHMe_2$), 27.25 and 24.37 (t, $NCH_2CH_2CH_2$), 19.42 and 17.73 (q, $CHMe$) and 13.81 (q, CH_2Me); the following peaks were observed for a minor amide rotamer (ratio ~5:1); δ_C 174.48 [s, C(O)NH], 138.13 (s, ArC_{ipso} of $BnOCH_2$), 127.60 (d, ArC), 73.26 and 71.01 (t, CH_2OCH_2), 56.89 and 55.46 [d, $CHNC(O)CHNH$], 45.58 (t, NCH_2CH_2), 28.51 and 21.49 (t, $NCH_2CH_2CH_2$) and 19.17 and 18.15 (q, $CHMe_2$); *m/z* 656 ($M^+ + 1$).

(S,S,R)-(−)-*Actinonin* **1**.—To a solution of (*S,S,R*)-(−)-*tribenzylactinonin* **35** (21 mg, 0.032 mmol) in methanol (5 cm^3) was added palladium(II) hydroxide (20% on charcoal) (5 mg). The resulting suspension was stirred under hydrogen (2 atm) at 26 °C for 4 h. The reaction mixture was then filtered through Celite and, after removal of the solvent, the residue was chromatographed on silica gel [ether–light petroleum (8:2); ether; then 4% methanol in ether] [R_f 0.45, Et_2O–MeOH (9:1)] to provide pure (*S,S,R*)-(−)-actinonin **1** (11 mg, 89%) as a solid, m.p. 103–105 °C; mixed m.p. 103–105 °C (lit.,[7] 104–105 °C); $[\alpha]_D^{23}$ −48.5 (*c* 0.15, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3200, 2680, 1740 and 1580; $\delta_H([^2H_5]$pyridine) 9.39 (1 H, d, *J* 8.9, CONH), 4.93 (1 H, t, *J* 8.6, CH_2OH), 4.56–4.48 (1 H, m, CHNH), 4.07 (1 H, dd, *J* 10.5 and 4.6, CHH'O), 4.04–3.98 (m, $NCHCH_2$), 3.83 (1 H, dd, *J* 10.5 and 6.4, CHH'O), 3.62–3.46 (2 H, m, NCH_2), 3.00 (1 H, dd, *J* 14.1 and 8.1, CHH'CO), 2.63 (1 H, dd, *J* 14.2 and 6.0, CHH'CO), 2.30–2.16 (1 H, m, COCH), 2.00–1.74 (4 H, m, $NCH_2CH_2CH_2$), 1.58–1.47 (1 H, m, $CHMe_2$), 1.42–1.22 (2 H, m, $CH_2[CH_2]_3Me$), 1.10–1.01 (12 H, m, $CHMe_2$ and $[CH_2]_3Me$) and 0.68 (3 H, t, *J* 7.0, CH_2Me); the following peaks were observed for a minor amide rotamer (ratio ~3:1): δ_H 9.27 (1 H, d, *J* 8.9, CONH), 5.14 (1 H, t, *J* 8.6, CH_2OH), 4.39–4.31 (1 H, m, CHNH) and 0.91 (3 H, d, CHMeMe); δ_C ($[^2H_5]$pyridine) 175.59 (s, C=O), 172.35 (s, C=O), 169.23 (s, C=O), 63.88 (t, CH_2OH), 60.37 and 57.08 [d, $CHNC(O)CHNH$], 48.19 (t, NCH_2), 43.52 (d, CH_2CHCO), 37.11 (t, CH_2CO), 33.29, 31.96, 27.29 and 22.75 (t, $[CH_2]_4$), 31.48 (d, $CHMe_2$), 27.80 and 24.67 (t, NCH_2CHCH_2), 19.75 and 18.76 (q, $CHMe_2$) and 14.07 (q, CH_2Me); the following peaks were observed for a minor amide rotamer (ratio ~4:1): δ_C 171.42 (s, C=O), 64.04 (t, CH_2OH), 60.14 and 56.75 [d, $CHNC(O)CHNH$], 32.66 (d, $CHMe_2$), 28.84 and 22.06 (t, $NCH_2CH_2CH_2$) and 19.45 and 18.99 (q, $CHMe_2$); *m/z* 386 ($M^+ + 1$).

(S,S,S)-epi-*Actinonin* **37**.—The above process was repeated at 12 °C on (S,S,S)-tribenzyl-*epi*-actinonin **36** (19 mg, 0.029 mmol) by using palladium(II) hydroxide (20% on charcoal) (5 mg) and the reaction mixture was stirred under hydrogen (5 atm) for 15 h to give, after chromatography [R_f 0.4, Et_2O–MeOH (9:1)] (S,S,S)-(−)-epi-*actinonin* **37** (11 mg, 98%) as a solid which went off-white after several days when left at room temperature; m.p. 92–93 °C; $[\alpha]_D^{20}$ −129.4 (*c* 1.35, MeOH) (Found: C, 59.15; H, 9.2. $C_{19}H_{35}N_3O_5$ requires C, 59.20; H, 9.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3230, 2650, 1742 and 1580; $\delta_H(CD_3OD)$ 8.13 (1 H, d, *J* 7.4, CONH), 4.40–4.34 (1 H, m, CHNH), 4.17–4.07 (1 H, m, $NCHCH_2$), 3.68–3.39 (4 H, m, NCH_2 and OCH_2), 2.84–2.75 (1 H, m, COCH), 2.33 (1 H, dd, *J* 14.6 and 7.5, CHH'O), 2.17 (1 H, dd, *J* 14.6 and 6.5, CHH'O), 2.10–1.85 (4 H, m, $NCH_2CH_2CH_2$), 1.63–1.48 (1 H, m, $CHMe_2$), 1.47–1.21 (8 H, m, $[CH_2]_4$), 0.99 (3 H, d, *J* 6.8, CHMeMe), 0.97 (3 H, d, *J* 6.8, CHMeMe) and 0.88 (3 H, t, CH_2Me); the following peaks were observed for a minor amide rotamer (ratio ~4:1): δ_H 8.02 (1 H, d, *J* 7.5, CONH), 4.61–4.55 (1 H, m, CHNH), 3.93–3.83 (1 H, m, $NCHCH_2$), 3.78 (1 H, dd, *J* 10.5 and 4.9, CHH'O), 2.35 (1 H, dd, *J* 14.8 and 7.6, CHH'CO), 1.01 (3 H, d, *J* 6.8, CHMeMe) and 0.95 (3 H, d, *J* 6.8, CHMeMe); $\delta_C([^2H_5]$pyridine) 175.88 (s, C=O), 172.40 (s, C=O), 169.19 (s, C=O), 63.94 (t, CH_2OH), 60.48 and 57.37 [d, $CHNC(O)CHNH$], 48.31 (t, NCH_2), 43.50 (d, CH_2CHCO), 37.15 (t, CH_2CO), 33.34, 32.13, 27.53 and 22.89 (t, $[CH_2]_4$), 31.47 (d, $CHMe_2$), 27.88 and 24.73 (t, $NCH_2CH_2CH_2$), 19.95 and 18.97 (q, $CHMe_2$) and 14.16 (q, CH_2Me); the following peaks were observed for a minor amide rotamer (ratio ~4:1): δ_C 171.50 (s, C=O), 64.12 (t, CH_2OH), 60.29 and 56.97 [d, $CHNC(O)CHNH$], 28.90 and 22.09 (t, $NCH_2CH_2CH_2$) and 19.62 and 19.12 (q, $CHMe_2$); *m/z* 386 ($M^+ + 1$).

Acknowledgements

We gratefully acknowledge financial support from NSERC of Canada (G. J. B.) and the SERC (G. B. and G. J. B.).

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Paper 2/05122B
Received 24*th September* 1992
Accepted 21*st October* 1992