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Asymmetric synthesis of tetrahydrolipstatin and valilactone

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ABSTRACT

The highly diastereoselective aldol reaction between acyl complexes of the iron chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] and β-hydroxy aldehydes (obtained via a Noyori asymmetric hydrogenation), followed by a tandem oxidative decomplexation–cyclisation process gives access to β-substituted and α,β-disubstituted β-lactones in high ee. This methodology has been employed in the asymmetric syntheses of tetrahydrolipstatin and valilactone.

1. Introduction

Over the past few decades, naturally occurring β-lactones (2-oxetanones) have received a great deal of interest as synthetic targets.[1] Lipstatin **1**, esterastin **2**, panclicin D **5** and valilactone **6** are pharmacologically active naturally occurring amino acid esters of δ-hydroxy-β-lactones which differ in the structure of the side chains and the amino acid residues attached (Fig. 1). These compounds and their analogues, such as tetrahydrolipstatin **3** and tetrahydroesterastin **4**, are potent esterase inhibitors and have shown utility as anti-obesity agents.[1] Their mode of action involves reversible inhibition of pancreatic lipase preventing cleavage of fatty acids from their triglyceride precursors such that fat travels through the digestive system without being absorbed into the body.[2] Lipstatin **1**, which was isolated from *Streptomyces toxytricini*,[3] and its non-natural derivative tetrahydrolipstatin **3** have also been shown to inhibit cholesterol esterase,[2b,4] and tetrahydrolipstatin **3** has since been developed into an anti-obesity drug (Orlistat®) due to its ease of preparation and greater stability over its naturally occurring analogue. To date, 4 formal syntheses,[5] 7 enantiospecific total syntheses[6] and 15 asymmetric total syntheses[7] of tetrahydrolipstatin **3** have been reported,[8] employing amongst other approaches asymmetric hydroboration,[7e] Prins cyclisation,[6f] [2+3]-cycloaddition,[7i] organocuprate addition[7c,g] and Sharpless asymmetric dihydroxylation.[7k,m] Valilactone **6**, which was isolated from *Streptomyces albolongus*,[9] has also been found to be a potent esterase inhibitor. To date only 1 enantiospecific total synthesis[10] and 2 asymmetric total syntheses[11] of valilactone **6** have been reported.

Previous investigations from this laboratory have shown that enolates derived from iron acyl complexes, incorporating the versatile iron chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)],[12] undergo highly diastereoselective reactions with a range of electrophiles. Subsequent activation via one-electron transfer converts the be-

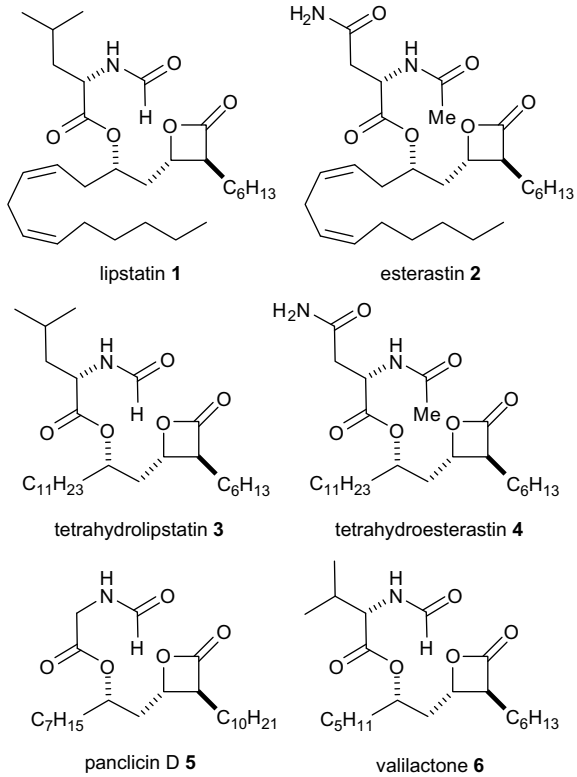

Figure 1. Naturally occurring β-lactones lipstatin **1**, esterastin **2** panclicidin D **5** and valilactone **6**, and non-natural derivatives tetrahydrolipstatin **3** and tetrahydroesterastin **4**.

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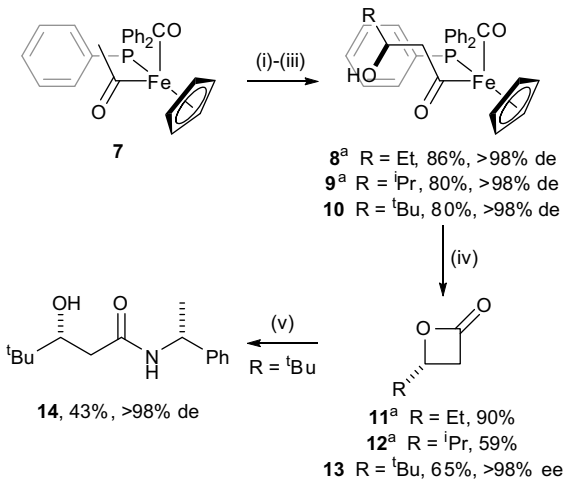
nign iron acyl species into a highly activated acyl donor, facilitating the synthesis of a range of homochiral carbonyl compounds,[13] including β-lactams[14] and β-lactones[15] derived from β-amino and β-hydroxy acyls, respectively. We report herein our full investigations concerning the highly stereoselective synthesis of β-lactones, which encompasses the extension of this methodology for the asymmetric total syntheses of tetrahydrolipstatin **3** and valilactone **6**. Parts of this work have been communicated previously.[7d,15]

2. Results and discussion

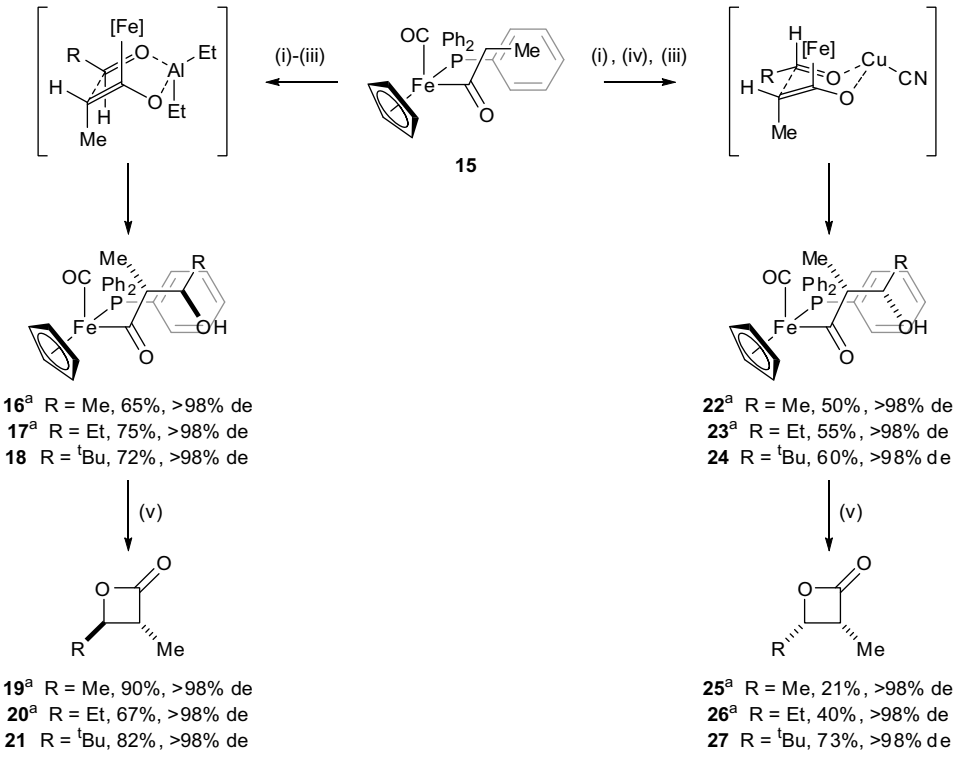
2.1. Model studies: asymmetric synthesis of β-substituted and α,β-disubstituted β-lactones

Initial studies were directed towards the synthesis of β-alkyl-substituted β-lactones. Treatment of the diethylaluminium enolate derived from homochiral iron acetyl complex (*S*)-**7**[16] with pivalaldehyde generated β-hydroxy acyl complex **10** in 80% yield and >98% de, with the stereochemical outcome of the aldol reaction being established via X-ray crystallography.[17] Subsequent oxidative decomplexation of **10** was achieved with bromine in CH_2Cl_2 at −78 °C to give homochiral β-lactone (*R*)-**13** in 65% yield. The absolute configuration of (*R*)-**13** was assigned from the known stereochemistry of precursor **10**, and the enantiopurity of (*R*)-**13** was determined to be >98% ee by derivatisation with (*R*)-α-methylbenzylamine[18] to give the corresponding amide (3*R*,α*R*)-**14** in >98% de. The generality of this protocol for the preparation of β-substituted-β-lactones was also established in the racemic series via reaction of the diethylaluminium enolate of **7** with propanal and 2-methylpropanal to give, after oxidative decomplexation, β-lactones **11** and **12** in good yield (Scheme 1).



Scheme 1. Reagents and conditions: (i) BuLi, −78 °C; (ii) Et_2AlCl, −40 °C; (iii) RCHO, −100 °C; (iv) Br_2, CH_2Cl_2, −78 °C, 15 min then Et_3N, −78 °C to rt; (v) (*R*)-α-methylbenzylamie, H_2O. ([a] Derived from racemic iron acetyl complex **7**.)

The synthesis of α,β-disubstituted β-lactones was next investigated via aldol reaction with enolates derived from iron propionyl complexes (Scheme 2). Treatment of the diethylaluminium (*Z*)-enolate derived from iron propionyl complex (*R*)-**15** with pivalaldehyde gave, after chromatographic purification, *anti*-aldol



Scheme 2. Reagents and conditions: (i) BuLi, −78 °C; (ii) Et_2AlCl, −40 °C; (iii) RCHO, −100 °C; (iv) CuCN, −40 °C; (v) Br_2, CH_2Cl_2, −78 °C, 15 min then Et_3N, −78 °C to rt. [[a] Derived from racemic iron acyl **15**; [Fe] = (η^5-C_5H_5)Fe(CO)(PPh_3).]

product **18** in 72% yield and >98% de, whereas treatment of the copper (*Z*)-enolate derived from (*R*)-**15** with pivalaldehyde and subsequent purification gave *syn*-aldol product **24** in 60% yield and >98% de. Subsequent oxidative decomplexation of **18** and **24** gave the corresponding *trans*- and *cis*-α,β-disubstituted-β-lactones **21** and **27** in 82 and 73% yield, respectively, and in >98% de in each case. The relative configurations within the lactones were established via ^{1}H NMR ^3J coupling constant analysis: *trans*-β-lactones have characteristic C(3)*H*–C(4)*H* coupling constants in the range 4.0–5.0 Hz, whereas the *cis*-β-lactones have coupling constants of approximately 6.5 Hz.[19] The generality of this protocol for the preparation of α,β-disubstituted β-lactones was also established in the racemic series using acetaldehyde and propanal to give β-lactones **19**, **20**, **25** and **26** in >98% de in each case. The outcome of this stereodivergent protocol is consistent with addition of the copper (*Z*)-enolate proceeding via a chair-like transition state to give the corresponding *syn*-addition products **22**–**24**, whereas the diethylaluminium (*Z*)-enolate traverses a boat-like transition state in which 1,3-strain between the sterically demanding iron auxiliary and the diethylaluminium unit is minimised to give the corresponding *anti*-addition products **16**–**18** (Scheme 2).[17]

With a reliable strategy for the synthesis of homochiral β-substituted and α,β-disubstituted β-lactones established, the application of this methodology towards the asymmetric total synthesis of tetrahydrolipstatin **3** and valilactone **6** was next investigated.

2.2. Application to the syntheses of tetrahydrolipstatin and valilactone

Retrosynthetic analyses of tetrahydrolipstatin **3** and valilactone **6** involved initial disconnection of the amino acid component to give the corresponding δ-hydroxy-β-lactones **28**. It was anticipated that δ-hydroxy-β-lactones **28** could result from oxidative decomplexation of iron acyl complexes **29**. In turn, iron acyl complexes **29** could be derived from a diastereoselective aldol reaction between a β-hydroxy aldehyde derivative **31** and iron octanoyl complex **30** (Fig. 2).

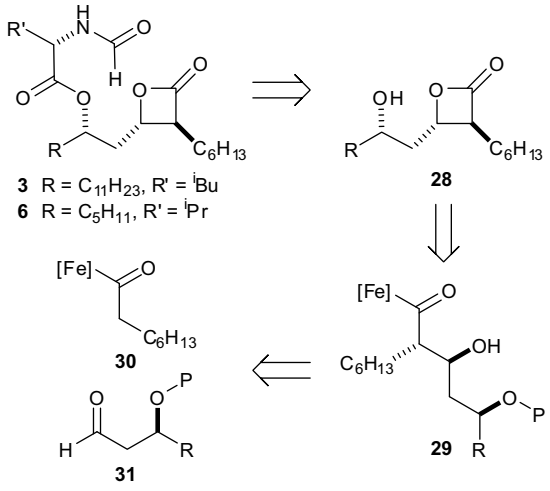
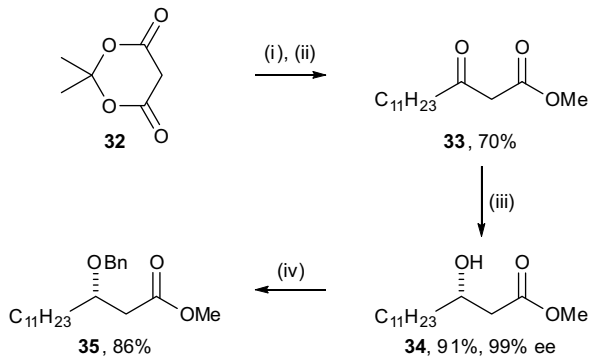


Figure 2. Retrosynthetic analysis of tetrahydrolipstatin **3** and valilactone **6**. [P = protecting group; [Fe] = Fe(η^5-C_5H_5)(CO)(PPh_3)].

It was therefore predicted that the development of an efficient asymmetric route to δ-hydroxy β-lactones **28**, and subsequent coupling with the requisite amino acid component would facilitate an entry to tetrahydrolipstatin **3** and valilactone **6**.

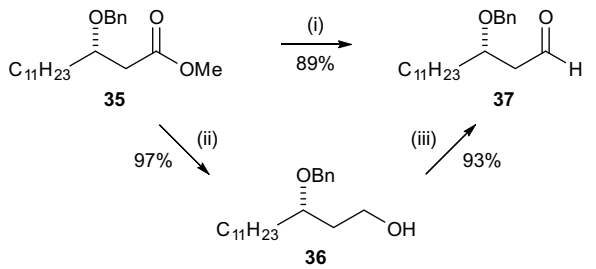
2.3. Asymmetric synthesis of tetrahydrolipstatin

The β-hydroxy aldehyde component required for the synthesis of tetrahydrolipstatin **3** was prepared from Meldrum's acid **32** in 4 steps, employing a Noyori catalytic asymmetric hydrogenation[20] of β-keto ester **33** as the key step. Thus, condensation of Meldrum's acid **32** with dodecanoyl chloride followed by methanolysis gave β-keto ester **33** in 70% yield, and reduction of β-keto ester **33** with Ru[(*S*)-BINAP]Cl_2, under 100 atm of H_2 for 3 days gave β-hydroxy ester (*S*)-**34** in 91% yield and 99% ee[21] {$[\alpha]_D^{23} = +17.9$ (*c* 1.3 in $CHCl_3$); lit.[22] for enantiomer $[\alpha]_D^{20} = -18.5$ (*c* 1.05 in $CHCl_3$)}. Subsequent O-protection with benzyltrichloroacetimidate and triflic acid gave (*S*)-**35** in 86% yield {$[\alpha]_D^{23} = +6.85$ (*c* 1.1 in $CHCl_3$); lit.[23] $[\alpha]_D^{20} = +3.5$ (*c* 1.1 in $CHCl_3$)} (Scheme 3).



Scheme 3. Reagents and conditions: (i) $C_{11}H_{23}COCl$, pyridine, CH_2Cl_2, 0 °C to rt, 2 h; (ii) MeOH, reflux, 5 h; (iii) Ru[(*S*)-BINAP]Cl_2, H_2 (100 atm), EtOH, rt, 68 h; (iv) benzyltrichloroacetimidate, CF_3SO_3H, cyclohexane/CH_2Cl_2 (2:1), rt.

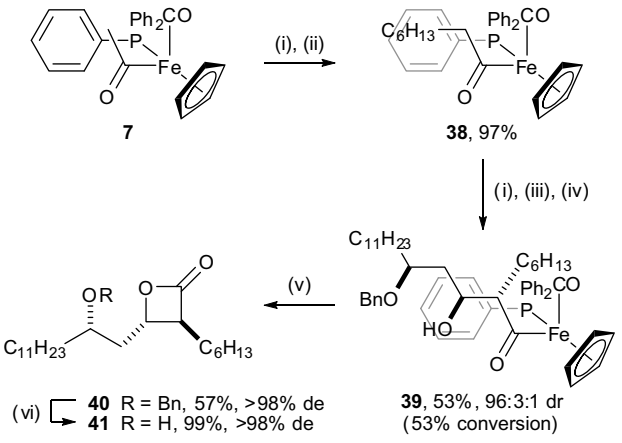
Conversion of the ester moiety within (*S*)-**35** to an aldehyde was achieved either by reduction with DIBAL-H in CH_2Cl_2 at −78 °C to give aldehyde (*S*)-**37** in 89% yield, or via reduction to the corresponding alcohol **36** with $LiAlH_4$, and then re-oxidation with Dess–Martin periodinane which afforded aldehyde (*S*)-**37** in comparable yield (90%) over two steps (Scheme 4).



Scheme 4. Reagents and conditions: (i) DIBAL-H, −78 °C, 1.5 h; (ii) $LiAlH_4$, Et_2O, 0 °C, 15 min; (iii) Dess–Martin periodinane, CH_2Cl_2, rt, 1.25 h.

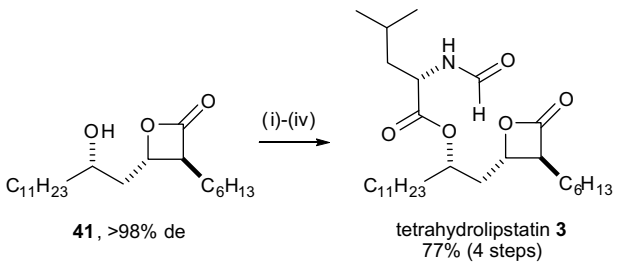
The diastereoselective aldol reaction of aldehyde (*S*)-**37** with an enolate derived from iron octanoyl complex **38** was next investigated. To achieve the desired stereochemical outcome for the synthesis of tetrahydrolipstatin **3** this strategy relied upon the powerful stereodirecting ability of the chiral iron auxiliary: aldol reactions employing aldehyde (*S*)-**37** are known to occur with moderate substrate bias towards generating the (*R*)-configuration at the β-stereocentre from *Si* facial attack on the aldehyde.[24] Previous investigations from within our laboratory concerning the asymmetric aldol condensation of iron acyl complexes with achiral aldehydes[13d,17,25] have indicated that the powerful stereocontrol of an iron acyl complex with an (*S*)-configuration would be required to overwhelm the moderate substrate bias of aldehyde (*S*)-**37**, and

achieve the desired (*S*)-configuration at the β-stereocentre in the product. Thus, octanoyl iron complex (*S*)-**38** was produced in 97% yield by alkylation of iron acetyl complex (*S*)-**7** via sequential treatment with BuLi and hexyl iodide. Deprotonation of (*S*)-**38** with BuLi at −78 °C and transmetallation with diethylaluminium chloride, and addition of aldehyde (*S*)-**37** gave 53% conversion to a 96:3:1 mixture[26] of diastereoisomeric β-hydroxy-α-alkyl iron complexes which were isolated in 53% yield, along with returned starting material **38** which was isolated in 39% yield. The configuration within the major diastereoisomeric product **39** was initially assigned by analogy to the established stereochemical outcome of aldol reactions employing chiral iron alkanoyl complexes, and was subsequently proven through conversion of **39** to tetrahydrolipstatin **3** (vide infra). Oxidative decomplexation of **39** gave, after column chromatography, protected β-lactone **40** in 57% yield as a single diastereoisomer (>98% de). The *trans*-configuration of the β-lactone moiety was confirmed by ^{1}H NMR ^3J coupling constant analysis ($J_{3,4}$ = 4.0 Hz).[19] The *O*-benzyl protecting group within **40** was next removed by catalytic hydrogenolysis to give alcohol **41** in 99% yield {$[\alpha]_D^{23} = -14.8$ (*c* 0.7 in CH_2Cl_2); lit.[27] $[\alpha]_D^{20} = -15.3$ (*c* 1.0 in CH_2Cl_2)} (Scheme 5).



Scheme 5. Reagents and conditions: (i) BuLi, THF, −78 °C, 30 min; (ii) $C_6H_{13}I$, −78 °C to rt, 4 h; (iii) Et_2AlCl, −40 °C, 2 h; (iv) (*S*)-**37**, −98 °C, 2 h then MeOH; (v) Br_2, CH_2Cl_2, −78 °C, 15 min then Et_3N, −78 °C to rt; (vi) H_2 (1 atm), Pd/C, CH_2Cl_2, rt, 12 h.

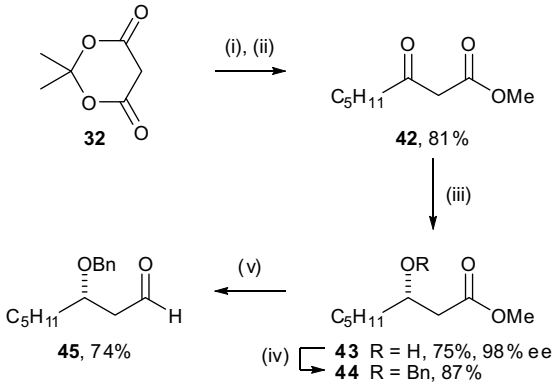
Addition of the *N*-formyl-substituted leucine component was carried out using standard methodology.[28] Alcohol **41** was coupled with *N*-Cbz L-leucine using DCC and a catalytic amount of DMAP. Removal of the *N*-Cbz-protecting group followed by formylation using acetic formic anhydride produced tetrahydrolipstatin **3** in 77% yield over four steps. Our synthetic sample of tetrahydrolipstatin was found to have identical spectroscopic properties to those of an authentic sample[29] {mp 40–41 °C; lit.[7a] mp 40–42 °C; $[\alpha]_D^{20} = -31.8$ (*c* 0.4 in $CHCl_3$); lit.[7a] $[\alpha]_D^{20} = -33$ (*c* 0.4 in $CHCl_3$)} (Scheme 6).



Scheme 6. Reagents and conditions: (i) Cbz-L-lucine, DCC, CH_2Cl_2, 0 °C, 15 min; (ii) DMAP, DMF, rt, 1.5 h; (iii) H_2 (1 atm), Pd/C, CH_2Cl_2, 6 h; (iv) AcOCHO, CH_2Cl_2, rt, 30 min.

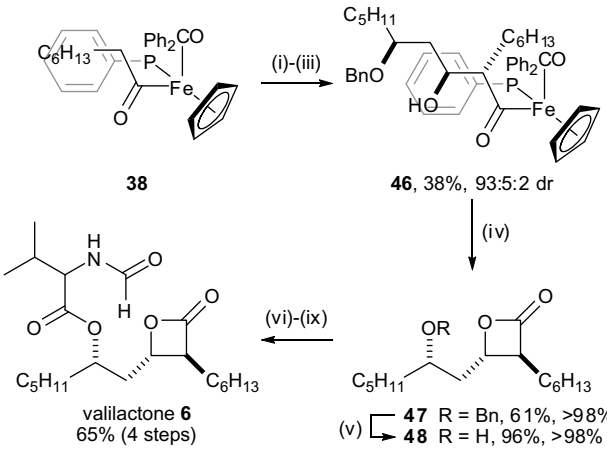
2.4. Asymmetric synthesis of valilactone

Following the same strategy as the synthesis of tetrahydrolipstatin **3**, condensation of Meldrum's acid **32** with hexanoyl chloride followed by methanolysis gave β-keto ester **42** in 81% yield. β-Keto ester **42** was subjected to catalytic asymmetric hydrogenation with Ru[(*S*)-BINAP]Cl_2, affording methyl (*S*)-3-hydroxyoctanoate **43** in 75% yield and 98% ee[30] {$[\alpha]_D^{20} = +22.5$ (*c* 1.1 in $CHCl_3$); lit.[31] $[\alpha]_D^{20} = +22.7$ (*c* 1.0 in $CHCl_3$)}, and recovered starting material **42** in 14% yield. Benzylation of **43** was carried out with benzyltrichloroacetimidate and triflic acid to give (*S*)-**44** in 87% yield. Subsequently, reduction of ester **44** was achieved using DIBAL-H to give aldehyde (*S*)-**45** in 74% yield (Scheme 7).



Scheme 7. Reagents and conditions: (i) $C_5H_{11}COCl$, pyridine, CH_2Cl_2, 0 °C; (ii) MeOH, reflux; (iii) Ru[(*S*)-BINAP]Cl_2, H_2 (100 atm), EtOH, rt; (iv) benzyltrichloroacetimidate, CF_3SO_3H, cyclohexane/CH_2Cl_2 (2:1), rt; (v) DIBAL-H, −78 °C.

The diastereoselective aldol reaction between aldehyde (*S*)-**45** and the diethylaluminium (*Z*)-enolate of iron acyl complex (*S*)-**38** gave a 93:5:2 mixture[32] of diastereoisomeric aldol products, which was isolated in 38% yield, along with recovered starting material **38**, isolated in 31% yield. The configuration within the major diastereoisomer **46** was initially assigned by analogy to the addition of the diethylaluminium (*Z*)-enolate of (*S*)-**38** to aldehyde (*S*)-**37** in the synthesis of tetrahydrolipstatin **3**, and was subsequently proven through conversion of **46** to valilactone **6** (vide infra). Treatment of **46** with bromine effected oxidative decomplexation



Scheme 8. Reagents and conditions: (i) BuLi, THF, −78 °C, 30 min; (ii) Et_2AlCl, −40 °C, 1 h; (iii) (*S*)-**45**, −98 °C, 2 h then MeOH; (iv) Br_2, CH_2Cl_2, −78 °C, 15 min then Et_3N, −78 °C to rt; (v) H_2 (1 atm), Pd/C, CH_2Cl_2, rt, 48 h; (vi) Cbz-L-valine, DCC, CH_2Cl_2, 0 °C, 15 min; (vii) DMAP, DMF, rt, 2 h; (viii) H_2 (1 atm), Pd/C, CH_2Cl_2, 8 h; (ix) AcOCHO, CH_2Cl_2, rt, 30 min.

and in situ lactonisation to afford β-lactone **47** in 61% yield as a single diastereoisomer (>98% de). The *trans*-configuration of the β-lactone moiety was established via ^{1}H NMR ^3J coupling constant analysis ($J_{3,4}$ = 4.0 Hz).[19] O-Deprotection of **47** was achieved by catalytic hydrogenolysis to give β-hydroxy lactone **48** in 96% yield ($J_{3,4}$ = 4.1 Hz) {$[\alpha]_D^{20} = -17.0$ (*c* 1.0 in $CHCl_3$); lit.[11a] $[\alpha]_D^{20} = -15.9$ (*c* 1.5 in $CHCl_3$)}. Conversion to valilactone **6** was achieved by coupling of **48** with *N*-Cbz L-valine using DCC and a catalytic amount of DMAP;[7a] subsequent hydrogenolysis and formylation with acetic formic anhydride gave valilactone **6** in 65% yield over four steps {$[\alpha]_D^{23} = -31.5$ (*c* 0.5 in $CHCl_3$); lit.[10] $[\alpha]_D^{23} = -32$ (*c* 0.3 in $CHCl_3$); lit.[11a] $[\alpha]_D^{23} = -33.7$ (*c* 0.1 in $CHCl_3$)} (Scheme 8).

3. Conclusion

In conclusion, the highly diastereoselective aldol reaction between chiral iron acyl complexes and β-hydroxy aldehydes has been used as the key step for asymmetric syntheses of tetrahydrolipstatin and valilactone in 12 and 10% overall yield, respectively (over 12 steps in both cases). This synthetic strategy should be widely applicable to the generation of homologues of this natural product family, with both different side chains and amino acid components, and other β-lactone natural products.

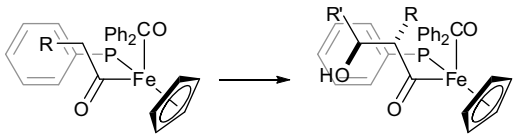
4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. CH_2Cl_2 was distilled from CaH_2 under a nitrogen atmosphere. THF was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Et_2O and toluene were dried over sodium. DMF was distilled form $MgSO_4$·EtOH was distilled from Mg turnings, activated by I_2. Methanol was distilled form CaH_2·H_2O was distilled. Pyridine and Et_3N were dried over KOH pellets and then distilled. BuLi was used as supplied as a solution in hexanes. Diethylaluminium chloride was used as supplied (Aldrich) as a solution in toluene. Bromine was dried by shaking with H_2SO_4 prior to distillation. All other solvents (analytical or HPLC grade) and reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$ or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

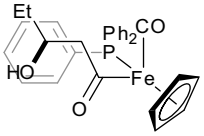
Elemental analyses were recorded by the microanalysis service of the Dyson Perrins Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a H_2O-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2/g and concentrations in g/100 mL. IR spectra were recorded on either a Perkin–Elmer 781 or Perkin–Elmer 1750 spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker 500, 300 or 200 MHz spectrometers in the deuterated solvent state. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

4.2. General procedure 1: aldol reaction with diethylaluminium enolates



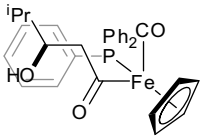
BuLi (1.5 equiv) was added to the requisite iron acyl complex (1.0 eq) in THF at −78 °C. The resulting solution was stirred at −78 °C for 45 min. Et_2AlCl (3.0 equiv) was added to the solution, which was then warmed to −40 °C and stirred for a further 2 h. The resultant solution was cooled to −100 °C, and a solution of aldehyde (2.0 equiv) in THF was added dropwise. After stirring at −100 °C for 2 h, MeOH was added. The mixture was then allowed to warm to rt and was concentrated in vacuo. The residue was re-dissolved in CH_2Cl_2 and filtered through Celite (eluent 30–40 °C petrol/Et_2O, 1:1). The residue was purified via chromatography on either silica or alumina to give the desired β-hydroxy iron acyl complex.

4.2.1. (*RS*)-Carbonyl(cyclopentadienyl)[(*RS*)-3-hydroxypentanoyl](triphenylphosphino)iron 8



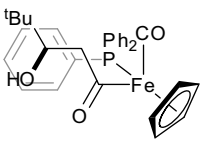
Following *general procedure* 1, **8** was produced in 86% yield; δ_H (500 MHz, $CDCl_3$) 0.75 (3H, m, C(5)H_3), 1.00–1.30 (2H, m, C(4)H_2), 2.70–3.30 (3H, m, C(2)H_2, C(3)H), 3.50 (1H, br s, OH), 4.45 (5H, s, C_5H_5), 7.30–7.65 (15H, m, *Ph*).

4.2.2. (*RS*)-Carbonyl(cyclopentadienyl)[(*SR*)-3-hydroxy-4-methylpentanoyl](triphenylphosphino)iron 9



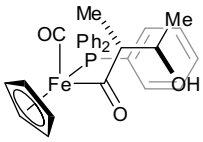
Following *general procedure* 1, **9** was produced in 80% yield; δ_H (500 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.8, CH(CH_3)$_A$(CH$_3$)$_B$), 0.75 (3H, d, *J* 6.8, CH(CH$_3$)$_A$(CH_3)$_B$), 1.15–1.37 (1H, m, CH(CH$_3$)$_2$), 2.70–2.95 (3H, m, C(2)H_2, C(3)H), 3.37 (1H, d, *J* 1.8, OH), 4.45 (5H, d, J_{PH} 1.1, C_5H_5), 7.32–7.58 (15H, m, *Ph*).

4.2.3. (*S*)-Carbonyl(cyclopentadienyl)[(*R*)-3-hydroxy-4,4-dimethylpentanoyl](triphenylphosphino)iron 10



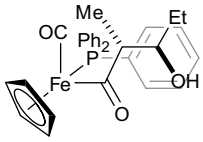
Following *general procedure* 1, **10** was produced in 80% yield; $[\alpha]_D^{25} = +82.4$ (*c* 0.2 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.72 (9H, s, C(CH_3)$_3$), 2.70–3.08 (3H, m, C(2)H_2, C(3)H), 3.32 (1H, s, OH), 4.45 (5H, d, J_{PH} 1.2, C_5H_5), 7.24–7.51 (15H, m, *Ph*).

4.2.4. (*RS*)-Carbonyl(cyclopentadienyl)[(2*RS*,3*RS*)-2-methyl-3-hydroxybutanoyl](triphenylphosphino)iron 16



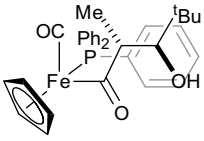
Following *general procedure* 1, **16** was produced in 65% yield; δ_H (500 MHz, $CDCl_3$) 0.39 (3H, d, *J* 7.0, C(2)CH_3), 1.08 (3H, d, *J* 6.3, C(4)H_3), 2.41 (1H, d, *J* 4.4, O*H*), 3.16 (1H, app quin, *J* 7.0, C(2)*H*), 3.78–3.86 (1H, m, C(3)*H*), 4.45 (5H, d, J_{PH} 1.1, C_5H_5), 7.32–7.71 (15H, m, *Ph*).

4.2.5. (*RS*)-Carbonyl(cyclopentadienyl)[(2*RS*,3*RS*)-2-methyl-3-hydroxypentanoyl](triphenylphosphino)iron 17



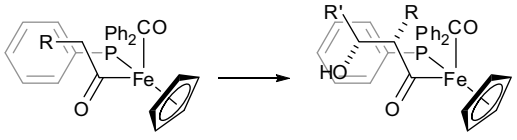
Following *general procedure* 1, **17** was produced in 75% yield; δ_H (500 MHz, $CDCl_3$) 0.39 (3H, d, *J* 7.0, C(2)CH_3), 0.95 (3H, t, *J* 7.7, C(5)H_3), 1.22–1.47 (2H, m, C(4)H_2), 2.45 (1H, br s, O*H*), 3.24 (1H, app quin, *J* 6.9, C(2)*H*), 3.55 (1H, m, C(3)*H*), 4.44 (5H, s, C_5H_5), 7.33–7.58 (15H, m, *Ph*).

4.2.6. (*R*)-Carbonyl(cyclopentadienyl)[(2*R*,3*S*)-2-methyl-3-hydroxy-4,4-dimethylpentanoyl](triphenylphosphino)iron 18



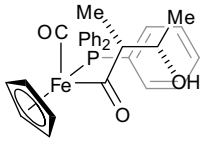
Following *general procedure* 1, **18** was produced in 72% yield; $[\alpha]_D^{25} = -210$ (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.51 (3H, d, *J* 6.7, C(2)CH_3), 0.92 (9H, s, C(CH_3)$_3$), 3.05–3.08 (1H, m, C(3)*H*), 3.20 (1H, d, *J* 3.2, O*H*), 3.61 (1H, app quin, *J* 7.2, C(2)*H*), 4.47 (5H, d, J_{PH} 0.9, C_5H_5), 7.33–7.61 (15H, m, *Ph*).

4.3. General procedure 2: addition to copper enolate



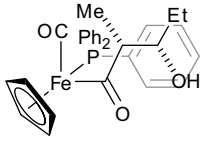
BuLi (1.2 equiv) was added to the requisite iron acyl complex (1.0 equiv) in THF at −78 °C. The resulting solution was stirred at −78 °C for 45 min before the addition of CuCN (3.0 equiv). The mixture was warmed to −40 °C and stirred for 2 h, then cooled to −78 °C, and a solution of aldehyde (2.0 equiv) in THF was added dropwise. After stirring at −78 °C for 2 h, MeOH was added. The mixture was then allowed to warm to rt and was concentrated in vacuo. The residue was re-dissolved in CH_2Cl_2 and filtered through Celite (eluent 30–40 °C petrol/Et_2O, 1:1). The residue was purified via chromatography on either silica or alumina to give the desired β-hydroxy iron acyl complex.

4.3.1. (*RS*)-Carbonyl(cyclopentadienyl)[(2*RS*,3*SR*)-2-methyl-3-hydroxybutanoyl](triphenylphosphino)iron 22



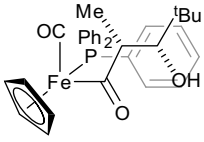
Following *general procedure* 2, **22** was produced in 50% yield; δ_H (500 MHz, $CDCl_3$) 0.26 (3H, d, *J* 6.9, C(2)CH_3), 1.06 (3H, d, *J* 6.5, C(4)H_3), 2.77 (1H, s, O*H*), 3.12 (1H, qd, *J* 6.9, 1.5, C(2)*H*), 4.27 (1H, qd, *J* 6.5, 1.5, C(3)*H*), 4.47 (5H, d, J_{PH} 1.0, C_5H_5), 7.35–7.57 (15H, m, *Ph*).

4.3.2. (*RS*)-Carbonyl(cyclopentadienyl)[(2*RS*,3*SR*)-2-methyl-3-hydroxypentanoyl](triphenylphosphino)iron 23



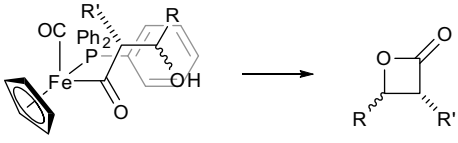
Following *general procedure* 2, **23** was produced in 55% yield; δ_H (500 MHz, $CDCl_3$) 0.19 (3H, d, *J* 6.9, C(2)CH_3), 0.95 (3H, t, *J* 7.5, C(5)H_3), 1.14–1.55 (2H, m, C(4)H_2), 2.68 (1H, s, O*H*), 3.18 (1H, app q, *J* 6.9, C(2)*H*), 4.00 (1H, t, *J* 6.8, C(3)*H*), 4.48 (5H, s, C_5H_5), 7.35–7.68 (15H, m, *Ph*).

4.3.3. (*R*)-Carbonyl(cyclopentadienyl)[(2*R*,3*R*)-2-methyl-3-hydroxy-4,4-dimethylpentanoyl](triphenylphosphino)iron 24



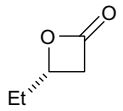
Following *general procedure* 2, **24** was produced in 60% yield; $[\alpha]_D^{20} = -129$ (*c* 0.25 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.23 (3H, d, *J* 6.9, C(2)CH_3), 0.95 (9H, s, C(CH_3)$_3$), 2.51 (1H, app d, *J* 2.0, O*H*), 3.40 (1H, app qd, *J* 6.9, 0.9, C(2)*H*), 3.66 (1H, app br t, *J* 1.5, C(3)*H*), 4.47 (5H, d, J_{PH} 1.2, C_5H_5), 7.34–7.55 (15H, m, *Ph*).

4.4. General procedure 3: decomplexation of β-hydroxy iron acyl complexes



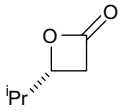
A solution of bromine (3.0 equiv) in CH_2Cl_2 was added to a solution of the requisite β-hydroxy iron acyl complex (1.0 equiv) in CH_2Cl_2 at −78 °C. The resultant solution was stirred for 15 min, excess Et_3N was added, and the mixture was allowed to warm to 10 °C before being concentrated in vacuo. The residue was extracted with CH_2Cl_2, and the resultant organic solution was allowed to stand, exposed to air, for 2 days before being filtered through alumina and concentrated in vacuo. The residue was purified via chromatography on either silica or alumina to give the desired β-lactone.

4.4.1. (*RS*)-4-Ethyloxetan-2-one 11



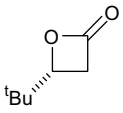
Following *general procedure* 3, **11** was produced in 90% yield; ν_{max} (film) 1832 (C=O); δ_H (500 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.4, CH_2CH_3), 1.75–1.90 (2H, m, CH_2CH_3), 3.06 (1H, dd, *J* 16.4, 5.7, C(3)H_AH_B), 3.46 (1H, dd, *J* 16.4, 4.2, C(3)H_AH_B), 4.43 (1H, m, C(4)*H*).

4.4.2. (*RS*)-4-Isopropyloxetan-2-one 12



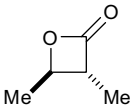
Following *general procedure* 3, **12** was produced in 59% yield; ν_{max} (film) 1820 (C=O); δ_H (500 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8, $CH(CH_3)_A(CH_3)_B$), 1.03 (3H, d, *J* 6.8, $CH(CH_3)_A(CH_3)_B$), 1.92 (1H, app oct, *J* 7.1, $CH(CH_3)_2$), 3.06 (1H, dd, *J* 16.3, 5.7, C(3)H_AH_B), 3.40 (1H, dd, *J* 16.3, 4.3, C(3)H_AH_B), 4.18 (1H, m, C(4)*H*).

4.4.3. (*R*)-4-*tert*-Butyloxetan-2-one 13



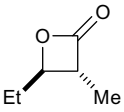
Following *general procedure* 3, **13** was produced in 65% yield; $[\alpha]_D^{25} = -12.6$ (*c* 0.7 in $CHCl_3$); {lit.[33] $[\alpha]_D^{20} = -20.7$ (*c* 2.0 in $CHCl_3$)}; ν_{max} (film) 1822 (C=O); δ_H (500 MHz, $CDCl_3$) 0.99 (9H, s, $C(CH_3)_3$), 3.16 (1H, dd, *J* 16.4, 5.9, C(3)H_AH_B), 3.31 (1H, dd, *J* 16.4, 4.5, C(3)H_AH_B), 4.25 (1H, dd, *J* 5.9, 4.5, C(4)*H*).

4.4.4. (3*RS*,4*RS*)-3,4-Dimethyloxetan-2-one 19



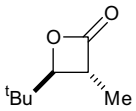
Following *general procedure* 3, **19** was produced in 90% yield; ν_{max} (film) 1820 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 7.6, C(3)CH_3), 1.56 (3H, d, *J* 6.5, C(4)CH_3), 3.22 (1H, qd, *J* 7.6, 3.9, C(3)*H*), 4.35 (1H, qd, *J* 6.5, 3.9, C(4)*H*).

4.4.5. (3*RS*,4*RS*)-3-Methyl-4-ethyloxetan-2-one 20



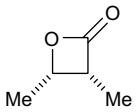
Following *general procedure* 3, **20** was produced in 67% yield; ν_{max} (film) 1820 (C=O); δ_H (500 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4, CH_2CH_3), 1.40 (3H, d, *J* 7.5, C(3)CH_3), 1.75–1.95 (2H, m, CH_2CH_3), 3.24 (1H, qd, *J* 7.5, 4.0, C(3)*H*), 4.11–4.17 (1H, m, C(4)*H*).

4.4.6. (3*R*,4*S*)-3-Methyl-4-*tert*-butyloxetan-2-one 21



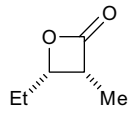
Following *general procedure* 3, **21** was produced in 82% yield; $[\alpha]_D^{25} = +33.1$ (*c* 0.3 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.00 (9H, s, $C(CH_3)_3$), 1.38 (3H, d, *J* 7.5, C(3)CH_3), 3.35 (1H, qd, *J* 7.5, 4.3, C(3)*H*), 3.91 (1H, d, *J* 4.3, C(4)*H*).

4.4.7. (3*RS*,4*SR*)-3,4-Dimethyloxetan-2-one 25



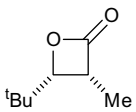
Following *general procedure* 3, **25** was produced in 21% yield; ν_{max} (film) 1832 (C=O); δ_H (500 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.4, C(3)CH_3), 1.45 (3H, d, *J* 6.4, C(4)CH_3), 3.74 (1H, app quin, *J* 7.4, C(3)*H*), 4.76 (1H, app quin, *J* 6.4, C(4)*H*).

4.4.8. (3*RS*,4*SR*)-3-Methyl-4-ethyloxetan-2-one 26



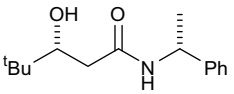
Following *general procedure* 3, **26** was produced in 40% yield; ν_{max} (film) 1821 (C=O); δ_H (500 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4, CH_2CH_3), 1.29 (3H, d, *J* 7.5, C(3)CH_3), 1.65–1.89 (2H, m, CH_2CH_3), 3.24 (1H, app quin, *J* 7.5, C(3)*H*), 4.45–4.52 (1H, m, C(4)*H*).

4.4.9. (3*R*,4*R*)-3-Methyl-4-*tert*-butyloxetan-2-one 27



Following *general procedure* 3, **27** was produced in 73% yield; $[\alpha]_D^{25} = +11.5$ (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1818 (C=O); δ_H (500 MHz, $CDCl_3$) 1.04 (9H, s, $C(CH_3)_3$), 1.40 (3H, d, *J* 7.9, C(3)CH_3), 3.36 (1H, m, C(3)*H*), 4.22 (1H, m, C(4)*H*).

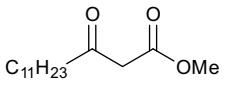
4.4.10. (*R*)-*N*-α-Methylbenzyl (*R*)-3-hydroxy-4,4-dimethylpentanamide 14



(*R*)-α-Methylbenzylamine (14 μL, 0.105 mmol) was added to an emulsion of β-lactone **13** (11.2 mg, 0.087 mmol) in H_2O (0.5 mL). The emulsion was stirred for 2 days before being extracted with

CH_2Cl_2 (4 × 1.5 mL). The organic extracts were concentrated in vacuo, and the residue was re-dissolved in EtOAc and filtered through a plug of silica (eluent EtOAc). The filtrate was concentrated in vacuo to give an oily residue which was purified via column chromatography (silica, eluent 30–40 °C petrol/EtOAc, 1:1) to give **14** as a colourless oil (8.0 mg, 37%); $[\alpha]_D^{20} = +94.6$ (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3850 (O–H), 1660, 1600 (C=O); δ_H (500 MHz, $CDCl_3$) 0.92 (9H, s, C(CH_3)$_3$), 1.51 (3H, d, *J* 7.0, C(α)CH_3), 2.23 (1H, dd, *J* 15.0, 10.5, C(2)H_AH_B), 2.37 (1H, dd, *J* 15.0, 2.0, C(2)H_AH_B), 3.45 (1H, s, O*H*), 3.68 (1H, app d, *J* 10.5, C(3)*H*), 5.15 (1H, quin, *J* 7.0, C(α)*H*), 6.10 (1H, br s, N*H*), 7.24–7.38 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8, 25.6, 34.5, 37.8, 48.8, 76.2, 126.2, 127.5, 128.8, 143.1, 172.1; *m*/*z* (CI^+) 249 ($[M]^+$, 100%); HRMS (CI^+) $C_{15}H_{23}NO_2^+$ ($[M]^+$) requires 249.1723; found 249.1728.

4.4.11. Methyl 3-oxotetradecanoate 33

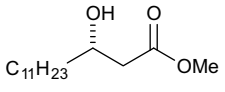


Lauroyl chloride (68 mL, 0.294 mol) was added to a solution of Meldrum's acid (40.0 g, 0.278 mol) and pyridine (45 mL, 0.556 mol) in CH_2Cl_2 (300 mL) at 0 °C over a period of 10 min. The reaction mixture was then allowed to warm to rt over 2 h whereupon the solution turned red and a white precipitate was formed. The mixture was then washed with 1.0 M aq HCl (3 × 100 mL) and H_2O (50 mL), and then dried, filtered and concentrated in vacuo. The residue was re-dissolved in MeOH (250 mL) and the resultant solution was heated at reflux for 5 h. After being allowed to cool to rt, the solution was concentrated in vacuo to give a white solid which was recrystallised from MeOH at −30 °C to give β-ketoester **33** as a white solid (53.7 g, 70%); mp 30–31 °C (lit.[34] mp 30 °C); ν_{max} (KBr) 1750, 1717 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.7, C(14)H_3), 1.58 (18H, m, 9 × CH_2), 2.52 (2H, t, *J* 7.4, C(4)H_2), 3.44 (2H, s, C(2)H_2), 3.73 (3H, s, OCH_3); *m*/*z* (ESI^+) 257 ($[M+H]^+$, 100%), 274 ($[M+NH_4]^+$, 80%).

4.4.12. Ru[(*S*)-BINAP](OAc)$_2$

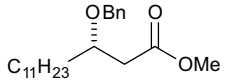
A solution of $RuCl_3$ hydrate (400 mg, 1.92 mmol) and 1,5-cyclooctadiene (0.8 mL, 6.52 mmol) in EtOH (2.0 mL) was heated at reflux for 5 h. The brown precipitate was recovered by filtration and washed with EtOH (1.0 mL) and Et_2O (1 mL). Et_3N (90 μL), degassed toluene (4.5 mL) and (*S*)-BINAP (100 mg, 0.161 mmol) were added, and the resultant mixture was heated at reflux for 12 h. After being allowed to cool to rt, the mixture was concentrated in vacuo to give an orange solid. This residue was dissolved in ^{t}BuOH (7.8 mL), and NaOAc (64 mg, 0.78 mmol) was added. The resultant mixture was heated at reflux for 12 h, allowed to cool to rt, and then concentrated in vacuo to give a yellow solid. The solid was extracted with Et_2O (3 × 3 mL) and the resulting solution was concentrated in vacuo. Re-extraction of the residue with degassed EtOH and removal of the solvent in vacuo gave a yellow powder. The powder was further purified via recrystallisation from hot ^{t}BuOH to give Ru[(*S*)-BINAP](OAc)$_2$ as a yellow powder.

4.4.13. Methyl (*S*)-3-hydroxytetradecanoate 34



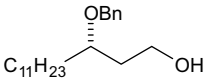
HCl (0.5 M in EtOH, 200 μL, 0.010 mmol) was added to a degassed solution of Ru[(*S*)-BINAP](OAc)$_2$ (40 mg, 0.048 mmol) in EtOH (8 mL) under an atmosphere of argon, and the resultant solution was stirred at rt for 2.5 h. A solution of methyl 3-oxotetradecanoate **33** (6.00 g, 23.0 mmol) in degassed EtOH (80 mL) was then added and the entire reaction mixture was transferred to a hydrogenation bomb, and an atmosphere of H_2 (100 atm) was applied for 68 h. The solution was then concentrated in vacuo and the residue was purified via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 2:1) to give alcohol (*S*)-**34** as a white solid (5.45 g, 91%); mp 34–35 °C (lit.[35] mp 39.5–40 °C); $[\alpha]_D^{20} = +17.9$ (*c* 1.3 in $CHCl_3$); {lit.[36] for enantiomer $[\alpha]_D^{20} = -17.1$ (*c* 1.0 in $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7, C(14)H_3), 1.22–1.63 (20H, m, 10 × CH_2), 2.42 (1H, dd, *J* 16.6, 8.9, C(2)H_A), 2.52 (1H, dd, *J* 16.6, 3.2, C(2)H_B), 2.87 (1H, d, *J* 1.7, O*H*), 3.72 (3H, s, OCH_3), 4.00 (1H, m, C(3)*H*).

4.4.14. Methyl (*S*)-3-benzyloxytetradecanoate 35



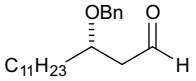
Benzyltrichloroacetimidate (2.35 g, 9.28 mmol) and alcohol (*S*)-**34** (2.00 g, 7.73 mmol) were dissolved in CH_2Cl_2/cyclohexane (1:2, 30 mL). Triflic acid (0.2 mL) was added to the solution, and a white precipitate was immediately formed, and the reaction mixture was stirred at rt for 1 h and was then filtered. The filtrate was washed with satd aq $NaHCO_3$ (25 mL) and H_2O (25 mL). The combined aqueous layers were extracted with CH_2Cl_2 (25 mL) and the combined organics were dried, filtered and concentrated in vacuo. Hexane (20 mL) was added to the residue and the resultant solution was filtered and then concentrated in vacuo. The residue was purified via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 12:1) to give **35** as a colourless oil (2.78 g, 86%); $[\alpha]_D^{20} = +6.85$ (*c* 1.1 in $CHCl_3$); {lit.[37] $[\alpha]_D^{20} = +3.5$ (*c* 1.1 in $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7, C(14)H_3), 1.27–1.64 (20H, m, 10 × CH_2), 2.49 (1H, dd, *J* 15.0, 5.3, C(2)H_A), 2.62 (1H, dd, *J* 15.0, 7.3, C(2)H_B), 3.68 (3H, s, OCH_3), 3.88 (1H, m, C(3)*H*), 4.54 (2H, app s, CH_2Ph), 7.25–7.35 (5H, m, *Ph*).

4.4.15. (*S*)-3-Benzyloxytetradecan-1-ol 36



A solution **35** (180 mg, 0.516 mmol) in anhydrous Et_2O (6 mL) was added to a suspension of $LiAlH_4$ (45 mg, 1.19 mmol) in anhydrous Et_2O (15 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 15 min, and then satd aq Na_2SO_4 (5 mL) was added and the reaction mixture was allowed to warm to rt. The aqueous layer was then extracted with Et_2O (5 mL), and the combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 5:1) to give **36** as a colourless oil (161 mg, 97%); $C_{21}H_{36}O_2$ requires C, 78.7; H, 11.3. Found: C, 78.75; H, 10.9; $[\alpha]_D^{20} = +32.3$ (*c* 1.45 in $CHCl_3$); {lit.[38] for enantiomer $[\alpha]_D^{20} = -30.9$ (*c* 1.1 in $CHCl_3$)}; ν_{max} (film) 3505, 3500 (O–H); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.6, C(14)H_3), 1.19–1.84 (22H, m, 11 × CH_2), 2.47 (1H, s, O*H*), 3.61–3.80 (3H, m, C(1)H_2, C(3)*H*), 4.49 (1H, d, *J* 11.4, CH_AH_BPh), 4.61 (1H, d, *J* 11.4, CH_AH_BPh), 7.25–7.35 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.0, 22.6, 25.0, 29.1, 29.3, 29.5, 29.7, 31.9, 33.3, 35.8, 60.8, 70.9, 78.7, 127.9, 128.1, 128.7, 138.6; *m*/*z* (ESI^+) 321 ($[M+H]^+$, 100%).

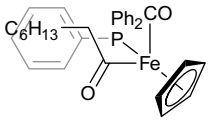
4.4.16. (*S*)-3-Benzyloxytetradecanal 37



Method A: Dess–Martin periodinane (1.65 g, 3.89 mmol) was added to a solution of alcohol (*S*)-**36** (940 mg, 2.93 mmol) in CH_2Cl_2 (30 mL) at rt. The resultant mixture was stirred for 1.25 h before the addition of Et_2O (40 mL) and 2.0 M aq NaOH (40 mL). The aqueous layer was extracted with Et_2O (40 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo to give **37** as a colourless oil (0.87 g, 93%); $[\alpha]_D^{20} = +32.3$ (*c* 1.45 in $CHCl_3$); ν_{max} (film) 1713; ν_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7, C(14)H_3), 1.17–1.69 (20H, m, 10 × CH_2), 2.62 (2H, m, C(2)H_2), 3.94 (1H, m, C(3)*H*), 4.50 (1H, d, *J* 11.5, C$H_A$$H_B$Ph), 4.58 (1H, d, *J* 11.5, CH$_A$$H_B$Ph), 7.26–7.37 (5H, m *Ph*), 9.80 (1H, t, *J* 2.2, C(1)*H*); *m*/*z* (ESI$^+$) 319 ([M+H]$^+$, 100%), 336 ([M+NH$_4$]$^+$, 70%).

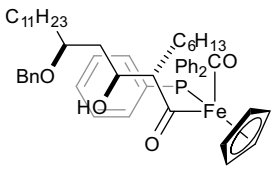
Method B: DIBAL-H (0.53 mL, 0.75 mmol) was added dropwise to a solution of **35** (235 mg, 0.67 mmol) in CH_2Cl_2 (25 mL) at −78 °C. After stirring for 1.5 h, satd aq NH_4Cl (0.3 mL) and 1.0 M aq HCl solution (0.5 mL) were sequentially added and the reaction mixture was allowed to warm to rt. H_2O (10 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 9:1) gave aldehyde (*S*)-**37** as a colourless oil (190 mg, 89%).

4.4.17. (*S*)-Carbonyl(cyclopentadienyl)octanoyl(triphenylphosphino)iron 38



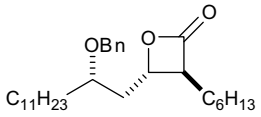
BuLi (1.44 mL, 3.6 mmol) was added to an orange solution of iron acetyl complex (*S*)-**7** (1.49 g, 3.28 mmol) in THF (30 mL). The resulting red solution was stirred for 30 min at −78 °C before the addition of hexyl iodide (0.97 mL, 6.56 mmol). Stirring was continued for 3 h at −78 °C, and then the reaction mixture was allowed to warm to rt and was concentrated in vacuo to afford a yellow oil. This residue was re-dissolved in CH_2Cl_2 (30 mL), filtered through Celite (eluent CH_2Cl_2) and concentrated in vacuo. The residue was purified via column chromatography (alumina, 30–40 °C petrol/CH_2Cl_2, 1:1) to give **38** as a yellow oil (1.71 g, 97%); $C_{32}H_{35}FeO_2P$ requires C, 71.4; H, 6.55; P, 5.75. Found: C, 71.4; H, 6.6; P, 5.9; $[\alpha]_D^{20} = +123.2$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1910, 1595 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 0.81–1.27 (13H, m, (CH_2)$_5$$CH_3$), 2.50–2.60 (1H, m, C(2)H_A), 2.81–2.91 (1H, m, C(2)H_B), 4.42 (5H, d, *J* 1.0, C$_5$$H_5$), 7.36–7.54 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.0, 22.6, 25.2, 29.2, 31.8, 66.2, 85.2, 127.9, 128.5, 129.6, 132.2, 133.4, 185.5; δ_P (160 MHz, $CDCl_3$) 72.6 (*P*Ph$_3$); *m*/*z* (CI$^+$) 538 ([M]$^+$, 100%).

4.4.18. (*S*)-Carbonyl(cyclopentadienyl)[(2*S*,3*S*,5*S*)-2-hexyl-3-hydroxy-5-benzyloxyhexadecanoyl](triphenylphosphino)iron 39



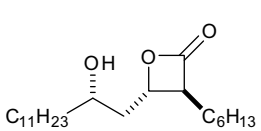
BuLi (0.24 mL, 0.34 mmol) was added to a yellow solution of iron complex (*S*)-**38** (119 mg, 0.221 mmol) in THF (30 mL). The resulting deep purple solution was stirred for 30 min at −78 °C before the addition of Et_2AlCl as a solution in THF (0.33 mL, 0.66 mmol). The reaction mixture was allowed to warm to −40 °C and stirring was continued for 2 h at −40 °C to produce a brown solution, which was cooled to −98 °C before the addition of aldehyde **37** (140 mg, 0.442 mmol) as a solution in THF (5 mL) over a period of 5 min. The resultant mixture was stirred at −98 °C for 2 h before being quenched with MeOH (1.0 mL). The resultant mixture was concentrated in vacuo, CH_2Cl_2 (30 mL) was added and the solution was filtered through Celite (eluent CH_2Cl_2). The filtrate was concentrated in vacuo to give a yellow oil, which was purified via column chromatography (alumina, 30–40 °C petrol/Et_2O, 1:1) to give recovered starting material **38** (500 mg, 92%) and **39** as a yellow oil (101 mg, 53%); $C_{53}H_{69}FeO_4P$ requires C, 74.3; H, 8.1; P, 3.6. Found: C, 74.3; H, 8.4; P, 3.7; ν_{max} (film) 3480 (O–H), 1995, 1910 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 0.68–1.74 (38H, m, 16 × CH_2, 2 × CH_3), 3.02 (1H, m, C(2)*H*), 3.57 (1H, d, *J* 3.7, O*H*), 3.62 (1H, m, C(3)*H*), 4.08–4.11 (1H, m, C(5)*H*), 4.33 (5H, d, *J* 1.2, C$_5$$H_5$), 4.51 (1H, d, *J* 11.5, C$H_A$$H_B$Ph), 4.62 (1H, d, *J* 11.5, CH$_A$$H_B$Ph), 7.23–7.57 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.0, 22.6, 24.9, 25.4, 27.1, 29.3, 29.6, 29.8, 29.9, 31.7, 31.9, 33.6, 38.6, 70.4, 70.5, 79.1, 85.7, 127.9, 129.5, 131.9, 133.5, 136.6, 221.2; δ_P (160 MHz, $CDCl_3$) 70.9 (*P*Ph$_3$); *m*/*z* (ESI$^+$) 857 ([M]$^+$, 100%).

4.4.19. (3*S*,4*S*,2′*S*)-3-Hexyl-4-(2′-benzyloxytridec-1′-yl)oxetan-2-one 40



A solution of Br_2 (12 μL, 0.24 mmol) in CH_2Cl_2 (1.0 mL) was added to a stirred solution of **39** (52 mg, 0.060 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 15 min before the addition of Et_3N (0.5 mL). The resultant green solution was allowed to warm to rt and was then concentrated in vacuo to yield a green solid. This residue was triturated with Et_2O (3 × 30 mL) to give a green oil after concentration of the organics in vacuo. Purification of the residue via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 7:1) gave **40** as a colourless oil (15.2 mg, 57%); $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9. Found: C, 77.9; H, 10.9; ν_{max} (film) 1828 (C=O); δ_H (500 MHz, $CDCl_3$) 0.85–2.20 (38H, m, 16 × CH_2, 2 × CH_3), 3.26 (1H, td, *J* 7.4, 4.0, C(3)*H*), 3.54 (1H, q, *J* 6.2, C(2′)*H*), 4.39–4.49 (1H, m, C(4)*H*), 4.44 (1H, d, *J* 11.5, C$H_A$$H_B$Ph), 4.56 (1H, d, *J* 11.5, CH$_A$$H_B$Ph), 7.12–7.38 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.0, 22.5, 22.7, 25.2, 26.8, 27.8, 29.3, 29.6, 31.5, 31.9, 33.5, 38.3, 56.7, 70.9, 75.2, 75.8, 127.7, 128.4, 138.4, 171.6; *m*/*z* (ESI$^+$) 445 ([M+H]$^+$, 100%).

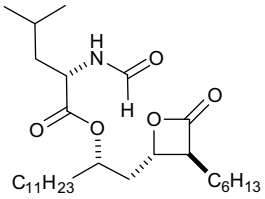
4.4.20. (3*S*,4*S*,2′*S*)-3-Hexyl-4-(2′-hydroxytridec-1′-yl)oxetan-2-one 41



A solution of **40** (18.5 mg, 0.042 mmol) in CH_2Cl_2 (5 mL) was stirred with Pd/C (5 mg) under H_2 (1 atm) for 12 h. The reaction mixture was then filtered through a pad of Celite (eluent CH_2Cl_2) and the filtrate was concentrated in vacuo to give alcohol **41** as a

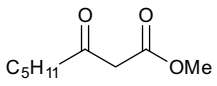
white solid (14.7 mg, 99%); mp 63 °C (lit.[5b] mp 63–64 °C); $[\alpha]_D^{20} = -14.8$ (*c* 0.7 in CH_2Cl_2); {lit.[27] $[\alpha]_D^{20} = -15.3$ (*c* 0.4 in $CHCl_3$)}; ν_{max} (KBr) 1815 (C=O); δ_H (500 MHz, $CDCl_3$) 0.81–0.95 (3H, m, CH_3), 1.04–2.08 (35H, m, 16 × CH_2, CH_3), 3.29–3.34 (1H, m, C(3)*H*), 3.72–3.79 (1H, m, C(2′)*H*), 4.45–4.51 (1H, m, C(4′)*H*).

4.4.21. (2*S*,2′*S*,3′*S*)-1-(3′-Hexyl-4′-oxooxetan-2′-yl)tridecan-2-yl (*S*)-*N*-formyl-leucinate [(−)-tetrahydrolipstatin] 3



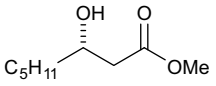
DCC (20 mg, 0.097 mmol) and (*S*)-*N*-Cbz-leucine (50 mg, 0.19 mmol) were stirred in CH_2Cl_2 (2.0 mL) at 0 °C for 15 min. The solvent was evaporated in vacuo, and the residue was dissolved in DMF (1.5 mL) and was added to a solution of **41** (6.6 mg, 0.019 mmol) and DMAP (3 mg) in DMF (1.0 mL). The reaction mixture was stirred at rt for 1.5 h. Addition of H_2O (1.0 mL) and extraction of the aqueous layer with Et_2O (4 × 3 mL) gave, after removal of the solvent in vacuo, a colourless oil. Purification of the residue by column chromatography (silica, eluent hexane/Et_2O, 3:1) produced an oil, which was subsequently stirred with Pd/C (10 mg) in CH_2Cl_2 under a H_2 atmosphere for 6 h. Filtration of the reaction mixture through a pad of Celite (eluent CH_2Cl_2) and concentration of the filtrate in vacuo gave a colourless oil, which was re-dissolved in CH_2Cl_2 (0.5 mL) and stirred with acetic formic anhydride (0.1 mL) for 30 min. Addition of H_2O (2 mL), extraction with CH_2Cl_2 (3 × 2 mL) and removal of the solvent in vacuo gave a colourless oil, which was purified via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) to give **3** as a white solid (7.1 mg, 77%); mp 40–41 °C (lit.[5b] mp 39–41 °C); $[\alpha]_D^{20} = -31.8$ (*c* 0.37 in $CHCl_3$); {lit.[7i] $[\alpha]_D^{20} = -32.0$ (*c* 0.7 in $CHCl_3$); lit.[6e] $[\alpha]_D^{20} = -32.6$ (*c* 1.0 in $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$) 0.89 (6H, m, C(13)H_3, C(6″)H_3), 0.98 (6H, m, CH(CH_3)$_2$), 1.18–1.85 (33H, m, 15 × CH_2, $CH_2CH(CH_3)_2$), 2.00 (1H, dt, *J* 14.7, 4.5, C(1)H_A), 2.15 (1H, dt, *J* 14.7, 7.8, C(1)H_B), 3.20 (1H, td, *J* 7.2, 4.0, C(3′)*H*), 4.28 (1H, m, C(3′)*H*), 4.67 (1H, td, *J* 9.3, 5.0, *CH*NH), 5.04 (1H, m, C(2)*H*), 5.93 (1H, d, *J* 8.8, N*H*), 8.23 (1H, s, *CH*O).

4.4.22. Methyl 3-oxooctanoate 42



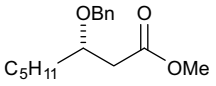
A solution of hexanoyl chloride (11.9 mL, 85.0 mmol) in CH_2Cl_2 (20 mL) was added to a solution of Meldrum's acid (12.5 g, 86.7 mmol) and pyridine (17.1 mL, 210 mmol) in CH_2Cl_2 (80 mL) at 0 °C over a period of 10 min. The reaction mixture was allowed to warm to rt over 1 h, and then stirred at rt for 14 h. The mixture was then washed with 2.0 M aq HCl (100 mL) and brine (50 mL), the aqueous layers were extracted with CH_2Cl_2 (2 × 50 mL), and then the combined organic extracts were dried, filtered and concentrated in vacuo. The residue was dissolved in MeOH (100 mL) and the resultant solution was heated at reflux for 3.5 h. After being allowed to cool to rt, the solution was concentrated in vacuo. The residue was purified via distillation (bp 120–122 °C at 23 mmHg) to give **42** as a colourless oil (12.1 g, 81%); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.6, C(8)H_3), 1.26–1.65 (6H, m, 3 × CH_2), 2.53 (2H, t, *J* 7.4, C(4)H_2), 3.46 (2H, s, C(2)H_2), 3.74 (3H, s, OCH_3).

4.4.23. Methyl (*S*)-3-hydroxyoctanoate 43



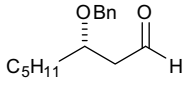
HCl (0.45 M in EtOH, 170 μL, 0.077 mmol) was added to a degassed solution of Ru[(*S*)-BINAP](OAc)$_2$ (30 mg, 0.036 mmol) in EtOH (10 mL) under an atmosphere of argon, and the resultant solution was stirred at rt for 2.5 h. A solution of **42** (6.00 g, 34.8 mmol) in degassed EtOH (50 mL) was then added, and the entire reaction mixture was transferred to a hydrogenation bomb and an atmosphere of H_2 (100 atm) was applied for 70 h. The solution was then concentrated in vacuo and the residue was purified via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 3:1) to give alcohol (*S*)-**43** as a colourless oil (4.53 g, 89%); $[\alpha]_D^{20} = +22.5$ (*c* 1.1 in $CHCl_3$); {lit.[39] $[\alpha]_D^{20} = +24$ (*c* 1.0 in $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.7, C(8)H_3), 1.28–1.61 (8H, m, 4 × CH_2), 2.43 (1H, dd, *J* 16.4, 3.2, C(2)H_A), 2.53 (1H, dd, *J* 16.4, 8.9, C(2)H_B), 2.88 (1H, br s, O*H*), 3.72 (3H, s, OCH_3), 4.01 (1H, m, C(3)*H*).

4.4.24. Methyl (*S*)-3-benzyloxyoctanoate 44



Benzyltrichloroacetimidate (5.48 g, 21.7 mmol) and **43** (3.15 g, 18.29 mmol) were dissolved in CH_2Cl_2/cyclohexane (1:2, 90 mL). Triflic acid (0.3 mL) was added to the solution and a white precipitate was immediately formed, and the reaction mixture was stirred at rt for 1.25 h before being filtered. The filtrate was washed with satd aq $NaHCO_3$ (50 mL) and H_2O (50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (50 mL) and the combined organics were dried, filtered and concentrated in vacuo. Hexane (20 mL) was added to the residue and the resultant solution was filtered and re-concentrated in vacuo. The residue was purified via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 9:1) to give **44** as a colourless oil (4.21 g, 87%); $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.15. Found: C, 73.0; H, 9.2; $[\alpha]_D^{20} = +7.11$ (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(8)H_3), 1.20–1.65 (8H, m, 4 × CH_2), 2.50 (1H, dd, *J* 15.0, 7.3, C(2)H_A), 2.62 (1H, dd, *J* 15.0, 5.4, C(2)H_B), 3.89 (1H, q, *J* 6.7, C(3)*H*), 4.55 (2H, s, CH_2Ph), 7.26–7.37 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.9, 22.4, 23.5, 31.7, 34.2, 39.6, 71.5, 76.4, 127.1, 127.7, 127.9, 128.4, 138.7, 172.5; *m*/*z* (ESI$^+$) 265 ([M+H]$^+$, 100%), 282 ([M+NH$_4$]$^+$, 60).

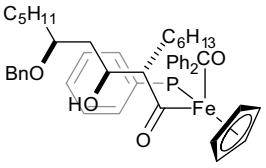
4.4.25. (*S*)-3-Benzyloxyoctanal 45



DIBAL-H (6.2 mL, 8.53 mmol) was added dropwise to a solution of **44** (1.88 g, 7.11 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After stirring for 45 min, satd aq NH_4Cl (4 mL) and 1.0 M aq HCl solution (4 mL) were sequentially added and the reaction mixture was allowed to

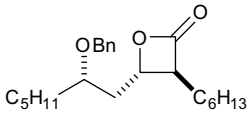
warm to rt. H_2O (10 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 7:1) gave **45** as a colourless oil (1.23 g, 74%); $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.5. Found: C, 77.1; H, 9.8; $[\alpha]_D^{20} = +14.1$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1710 (C=O); δ_H (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.8, C(8)H_3), 1.25–1.76 (8H, m, 4 × CH_2), 2.58 (1H, dd, *J* 16.3, 7.2, C(2)H_A), 2.68 (1H, dd, *J* 16.3, 4.8, C(2)H_B), 3.96 (1H, m, C(3)*H*), 4.53 (1H, d, *J* 16.7, CH_AH$_B$Ph), 4.57 (1H, d, *J* 16.7, CH$_A$$H_B$Ph), 7.14–7.39 (5H, m, *Ph*), 9.81 (1H, t, *J* 2.2, C*H*O); δ_C (125 MHz, $CDCl_3$) 13.8, 22.4, 24.6, 31.7, 34.0, 48.2, 71.2, 74.3, 127.8, 127.9, 128.2, 128.6, 138.4; *m*/*z* (ESI^+) 252 ($[M+NH_4]^+$, 70%), 235 ($[M+H]^+$, 100).

4.4.26. (*S*)-Carbonyl(cyclopentadienyl)[(2*S*,3*S*,5*S*)-2-hexyl-3-hydroxy-5-benzyloxydecanoyl] (triphenylphosphino)iron 46



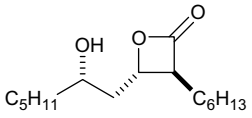
BuLi (1.1 mL, 2.75 mmol) was added to a yellow solution of **38** (1.02 g, 1.89 mmol) in THF (50 mL). The resulting deep purple solution was stirred for 30 min at −78 °C before the addition of Et_2AlCl as a solution in THF (2.8 mL, 5.6 mmol). The reaction mixture was allowed to warm to −40 °C. Stirring was continued for 1 h at −40 °C, affording a brown solution which was cooled to −98 °C before the addition of **45** (0.72 g, 3.07 mmol) as a solution in THF (5 mL) over a period of 5 min. The mixture was stirred at −98 °C for 2 h before being quenched with MeOH (1.0 mL). The resultant mixture was concentrated in vacuo, CH_2Cl_2 (30 mL) was added and the solution was filtered through Celite (eluent CH_2Cl_2). The filtrate was concentrated in vacuo to give a yellow oil, which was purified via column chromatography (silica, 30–40 °C petrol/Et_2O, 5:1) to give recovered starting material **38** (316 mg, 31%) and **46** as a yellow oil (542 mg, 38%); $C_{47}H_{57}FeO_4P$ requires C, 73.05; H, 7.4; P, 4.0. Found: C, 72.9; H, 7.5; P, 4.3; ν_{max} (film) 1905, 1575 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 0.66–1.75 (26H, m, 10 × CH_2, 2 × CH_3), 3.02 (1H, m, C(2)*H*), 3.65–3.59 (2H, m, C(3)*HOH*), 4.10–4.13 (1H, m, C(5)*H*), 4.33 (5H, d, *J* 1.2, C_5H_5), 4.52 (1H, d, *J* 11.6, CH_AH$_B$Ph), 4.62 (1H, d, *J* 11.6, CH$_A$$H_B$Ph), 7.28–7.58 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.9, 22.5, 24.4, 25.2, 26.9, 29.9, 31.6, 31.9, 32.0, 33.3, 38.1, 70.4, 70.5, 77.6, 79.1, 85.8, 127.9, 129.5, 132.2, 133.5, 136.6, 138.6; δ_P (160 MHz, $CDCl_3$) 70.9 (*P*Ph_3); *m*/*z* (ESI^+) 773 ($[M]^+$, 100%).

4.4.27. (3*S*,4*S*,2′*S*)-3-Hexyl-4-(2′-benzyloxyhept-1′-yl)oxetan-2-one 47



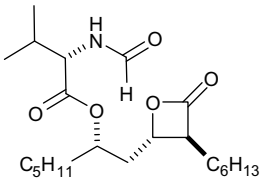
A solution of Br_2 (60 μL, 1.18 mmol) in CH_2Cl_2 (2.0 mL) was added to a stirred solution of **46** (458 mg, 0.59 mmol) in anhydrous CH_2Cl_2 (80 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 15 min before the addition of Et_3N (0.8 mL). The resultant green solution was allowed to warm to rt and was then concentrated in vacuo to yield a green solid. This residue was triturated with Et_2O (3 × 30 mL) to give a green oil after concentration of the organics in vacuo. Purification of the residue via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 6:1) gave **47** as a colourless oil (130 mg, 61%); $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.0. Found: C, 76.8; H, 10.0; $[\alpha]_D^{20} = -2.45$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1805 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87–2.23 (26H, m, 10 × CH_2, 2 × CH_3), 3.26 (1H, td, *J* 7.7, 4.0, C(3)*H*), 3.55 (1H, q, *J* 5.6, C(2′)*H*), 4.41–4.47 (1H, m, C(4)*H*), 4.45 (1H, d, *J* 11.5, CH_AH$_B$Ph), 4.57 (1H, d, *J* 11.5, CH$_A$$H_B$Ph), 7.28–7.39 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.9, 22.4, 24.6, 26.6, 27.6, 28.8, 31.3, 31.7, 33.2, 38.0, 56.6, 70.7, 75.2, 75.7, 127.1, 127.8, 128.6, 138.5, 171.9; *m*/*z* (ESI^+) 378 ($[M+NH_4]^+$, 80%), 361 ($[M+H]^+$, 100).

4.4.28. (3*S*,4*S*,2′*S*)-3-Hexyl-4-(2′-hydroxyhept-1′-yl)oxetan-2-one 48



A solution of β-lactone **47** (110 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) was stirred with Pd/C (50 mg) under an atmosphere of H_2 (1 atm) for 48 h. The reaction mixture was then filtered through a pad of Celite (eluent CH_2Cl_2) and the filtrate was concentrated in vacuo. Purification of the residue via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 3:1) gave **48** as a white solid (79 mg, 96%); $C_{16}H_{30}NO_3$ requires C, 71.1; H, 11.2. Found: C, 71.0; H, 11.5; mp 31 °C; $[\alpha]_D^{20} = -17.0$ (*c* 1.0 in $CHCl_3$); {lit.[11a] $[\alpha]_D^{20} = -15.9$ (*c* 1.5 in $CHCl_3$)}; ν_{max} (KBr) 1810 (C=O); $=_H$ (500 MHz, $CDCl_3$) 0.86–2.07 (26H, m, 10 × CH_2, 2 × CH_3), 3.31 (1H, dd, *J* 5.6, 4.0, C(3)*H*), 3.74–3.82 (1H, m, C(2′)*H*), 4.47 (1H, td, *J* 6.6, C(4)*H*); δ_C (125 MHz, $CDCl_3$) 13.8, 22.4, 25.0, 26.6, 27.6, 28.8, 31.3, 31.5, 37.5, 41.0, 56.6, 69.2, 76.2, 171.7; *m*/*z* (ESI^+) 271 ($[M+H]^+$, 100).

4.4.29. (2*S*,2′*S*,3′*S*)-1-(3′-Hexyl-4′-oxooxetan-2′-yl)heptan-2-yl (*S*)-*N*-formyl-valinate [(−)-valilactone] 6



DCC (184 mg, 0.89 mmol) and (*S*)-*N*-Cbz-valine (421 mg, 1.78 mmol) were stirred in CH_2Cl_2 (7.0 mL) at 0 °C for 15 min. The solvent was evaporated in vacuo, and the residue was dissolved in DMF (6.0 mL) and added to a solution of **48** (48 mg, 0.178 mmol) and DMAP (18 mg) in DMF (1.0 mL). The reaction mixture was stirred at rt for 1.5 h. Addition of H_2O (1.0 mL) and extraction of the aqueous layer with Et_2O (4 × 3 mL) gave, after removal of the solvent in vacuo, a colourless oil. Purification of the residue by column chromatography (silica, eluent hexane/Et_2O, 3:1) produced an oil, which was subsequently stirred with Pd/C (50 mg) in CH_2Cl_2 under a H_2 atmosphere for 8 h. Filtration of the reaction mixture through a pad of Celite (eluent CH_2Cl_2) and concentration of the filtrate in vacuo gave a colourless oil, which was re-dissolved in CH_2Cl_2 (1.0 mL) and stirred with acetic formic anhydride (0.2 mL) for 30 min. Addition of H_2O (2 mL), extraction

with CH_2Cl_2 (3 × 2 mL) and removal of the solvent in vacuo gave a colourless oil, which was purified via column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) to give **6** as a white solid (45 mg, 65%); mp 55–56 °C (lit.[40] mp 55–56 °C); $[\alpha]_D^{20} = -31.5$ (*c* 0.5 in $CHCl_3$); {lit.[10] $[\alpha]_D^{23} = -32$ (*c* 0.3 in $CHCl_3$); lit.[36] $[\alpha]_D^{23} = -33.7$ (*c* 0.1 in $CHCl_3$)}; ν_{max} (KBr) 3430 (N–H), 1820, 1725, 1690 (3 × C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (6H, m, C(7)H_3, C(6″)H_3), 0.91 (3H, d, *J* 6.9, CH(CH_3)$_A$), 0.98 (3H, d, *J* 6.9, CH(CH_3)$_B$), 1.23–1.44 (14H, m, 7 × CH_2), 1.56–1.82 (4H, m, 2 × CH_2), 2.01 (1H, m, C*H*(CH_3)$_2$), 2.20 (2H, m, C(1)H_2), 3.22 (1H, td, *J*, 7.9, 4.0, C(3′)*H*), 4.28 (1H, m, C(2′)*H*), 4.61 (1H, dd, *J* 9.0, 4.8, C*H*NH), 5.01 (1H, m, C(2)*H*), 6.24 (1H, d, *J* 8.8, N*H*), 8.25 (1H, s, C*H*O); δ_C (125 MHz, $CDCl_3$) 13.8, 13.9, 17.4, 19.2, 22.3, 22.4, 24.7, 26.6, 27.6, 28.9, 30.9, 31.4, 33.8, 38.6, 55.9, 57.0, 72.8, 74.5, 160.9, 170.8.

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