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Formal Synthesis of the Anti-Angiogenic Polyketide (−)-Borrelidin under Asymmetric Catalytic Control

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Abstract: Borrelidin (**1**) is a polyketide that possesses extremely potent anti-angiogenesis activity. This paper describes its formal total synthesis by the most efficient route to date. This modular approach takes optimal benefit of asymmetric catalysis and permits the synthesis of analogues; in addition, the high yields and selectivities obtained eliminate the need for separation of stereoisomers. The upper half of borrelidin has been accessed by iterative copper-catalysed asymmetric conjugate addition of methylmagnesium bromide, whereas synthesis of the lower half of the molecule was achieved by relying on asymmetric hydrogenation and cross-methathesis as key steps.

Keywords: asymmetric catalysis · conjugate addition · hydrogenation · polyketides · total synthesis

Introduction

Nature's bounty of molecules possessing inherent medicinal value has changed the world.[1] Borrelidin (**1**), isolated by Berger and co-workers in 1949 from *Streptomyces rochei*,[2] is a molecule that exhibits a host of potent physiological activities. The properties of borrelidin include anti-bacterial[3] activity involving selective inhibition of threonyl-tRNA synthetase,[4] anti-viral activity,[5] anti-malarial activity against chloroquine-resistant strains[6] and the inhibition of cyclin-dependent kinase Cdc28/Cln2 in *Saccharomyces cerevisiae*.[7] Most importantly, however, borrelidin exhibits a sub-nanomolar IC_{50} value for the inhibition of angiogenesis.[8] It is this latter activity that is very important for anti-cancer research. Although borrelidin is currently obtained in small amounts by fermentation, its high cost limits the full exploration of its possibilities in biological and medical research. Keller-Schierlein and co-workers elucidated the planar architecture of **1** by means of chemical degradation;[9] this work was followed by Anderson et al. who assigned the absolute configuration of the stereocentres by X-ray crystallography.[10]

Results and Discussion

The dense arrangement of chiral centres in this 18-membered macrocycle, together with the peculiar and sensitive *Z*,*E*-cyanodiene moiety, has attracted considerable attention from organic chemists.[11] After an early study by Haddad et al.,[12] the groups of Morken[13] and Hanessian[14] first reported total syntheses of the compound, closely followed by the groups of Theodorakis[15] and Omura.[16] The strategies reported essentially rely on starting materials from the chiral pool, chiral auxiliaries or kinetic resolution of advanced intermediates.[17] In the retrosynthesis applied by Omura and co-workers,[16] **1** is disconnected into two parts (Scheme 1). The upper part (**A**) contains the poly-1,3-methyl array and a deoxypropionate unit flanked by two hydroxy groups. The lower part (**B**) contains a disubstituted cyclopentyl motif together with a *Z*,*E*-cyanodiene unit. Negishi and co-workers[18] and Herber and Breit[19] achieved the synthesis of part **A** by an iterative catalytic approach and a chiral-reagent-based strategy, respectively. In view of the need for a more efficient and cost-effective synthesis of borrelidin and its derivatives, we were challenged to develop a route in which all formed chiral centres would be under catalyst control. This "catalytic total synthesis" should lead to a significantly improved overall yield and avoid the tedious separation of diastereomers.

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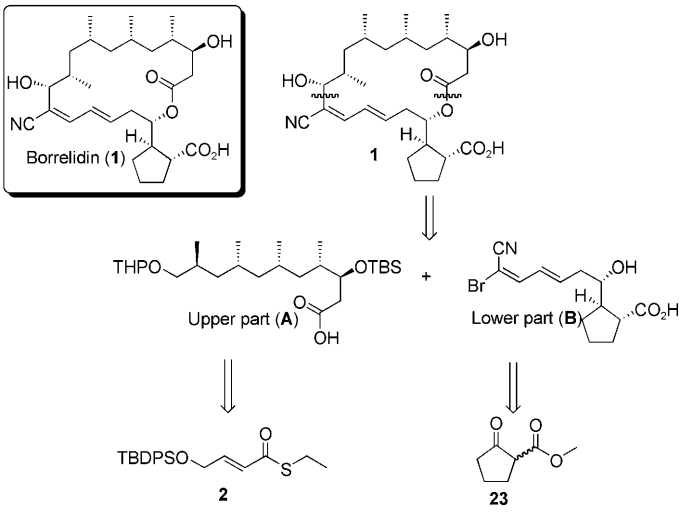
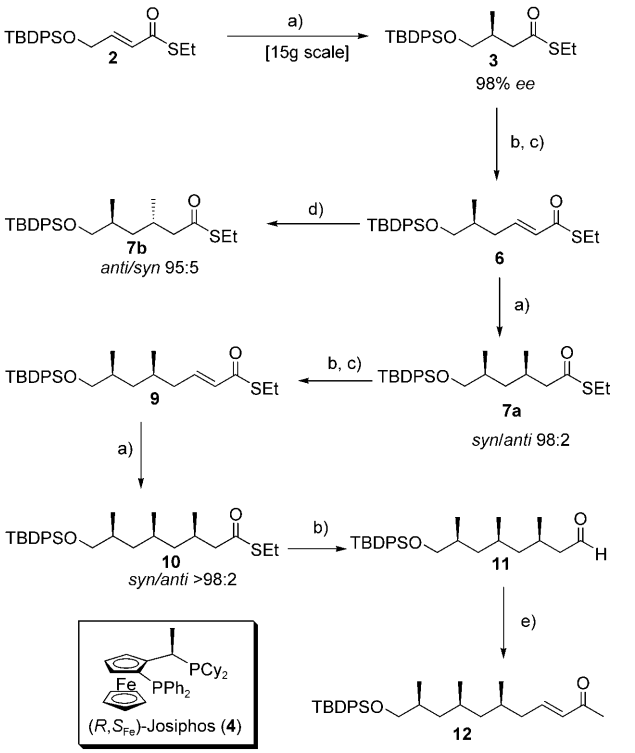
Supporting information for this article (chromatograms, experimental procedures for remaining compounds and spectra for all compounds) is available on the WWW under http://dx.doi.org/10.1002/chem.201001284.



Scheme 1. Retrosynthesis of borrelidin (**1**). TBS: *tert*-butyldimethylsilyl; TBDPS: *tert*-butyldiphenylsilyl; THP: tetrahydropyranyl.

The disconnection into upper part **A** and lower part **B** was adopted. For part **A**, we were keen to apply our iterative catalytic asymmetric conjugate-addition approach. This has proven its effectiveness in the total synthesis of a variety of natural products containing all-*syn* deoxypropionate units.[20] Particularly challenging would be the introduction of a methyl group with 1,3-*anti* stereochemistry at the left end of **A**, after three *syn*-methyl groups, owing to the intrinsic substrate preference for an all-*syn* array.[21] The β-hydroxy acid unit was planned to be derived from the corresponding keto ester through asymmetric hydrogenation. In the reported synthesis of part **B**, the disubstituted cyclopentyl fragment has been invariably prepared by using a chiral auxiliary, for example, menthol, or through kinetic resolution. This, however, requires a lengthy synthesis route with moderate overall yields. It was envisioned that, by starting with **23**, asymmetric hydrogenation would install both chiral centres at once in an *anti* relationship. Although the reported enantioselectivities were not sufficient, this presented an appealing opportunity and would translate to a significant improvement in the synthesis. Finally, we planned a challenging alkene metathesis in the synthesis of the cyanodiene fragment.

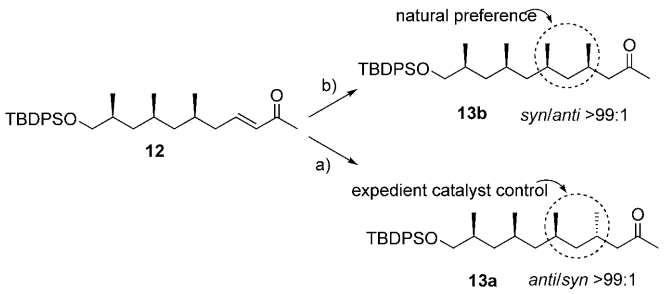
Earlier work by our group has demonstrated that the Cu/Josiphos-catalysed (Josiphos: structure in Scheme 2) iterative asymmetric conjugate addition of MeMgBr leads to excellent stereochemical control in the synthesis of 1,3-methyl arrays. This has been successfully exploited in the first total synthesis of mycocerosic acid and phthioceranic acid.[22] On the basis of this efficient and robust methodology, **2** (Scheme 2) was chosen as the starting material because it possesses a protected hydroxy function at the terminus of the unsaturated thioester, which remains inert under the iterative reaction conditions (conjugate addition, DIBALH reduction and Wittig or Horner–Wadsworth–Emmons (HWE) reaction). **2** is conveniently prepared from ethylene glycol in three steps.



Scheme 2. Synthesis of the upper part (**A**) of borrelidin (**1**). Reagents and conditions: a) MeMgBr (1.2 equiv), **4**/CuBr (1 mol%), *t*BuOMe, −78°C, 18 h; 96%, 98% *ee* for **3**; 90%, *syn*/*anti* 98:2 for **7a**; 87%, *syn*/*anti* >98:2 for **10**; b) DIBALH, CH_2Cl_2, −65°C, 4 h; c) $(EtO)_2OPCH_2COSEt$, *n*BuLi, THF, RT, 10 h; 81% over 2 steps; d) MeMgBr, *ent*-**4**/CuBr (1 mol%), *t*BuOMe, −78°C, 18 h; 89%, *anti*/*syn* 95:5; e) $(EtO)_2OPCH_2COMe$, *n*BuLi, THF, RT, 10 h; 92% over 2 steps. Cy: cyclohexyl; DIBALH: diisobutylaluminium hydride; THF: tetrahydrofuran.

Substrate **2** (Scheme 2) gives excellent yield and enantioselectivity (96%, 98% *ee*) and complete regioselectivity in the 1,4 addition of MeMgBr with 1 mol% CuBr/**4**. The reaction was conveniently carried out on a 15 g scale. Bifunctional building block **3** was reduced to the corresponding aldehyde **5** (see the Supporting Information), and this was followed by a HWE reaction to give thioester **6**. The nearly exclusive *syn* selectivity (*syn*/*anti* 98:2) of the second conjugate addition, leading to dimethyl thioester **7a**, was deduced from the ^{1}H NMR spectrum through comparison with the spectrum of the *anti*-dimethyl thioester **7b**, prepared by using *ent*-**4** (Scheme 2). By repeating this sequence of reduction, HWE olefination with $(EtO)_2OPCH_2COSEt$ and 1,4 addition once more, the third methyl group was introduced in a *syn* fashion to give **10** in 87% yield after isolation and with a *syn*/*anti* ratio of >98:2. Reduction of **10** with DIBALH afforded aldehyde **11**, and a subsequent HWE reaction with $(EtO)_2OPCH_2COMe$ resulted in α,β-unsaturated ketone **12**.

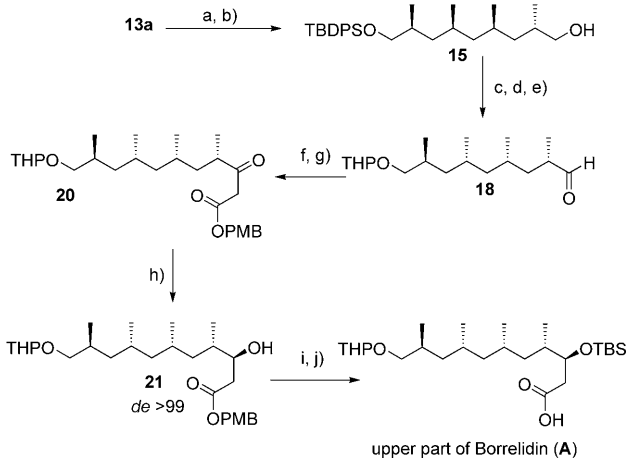
We were pleased to see that, with CuBr/*ent*-**4** as the catalyst, the introduction of the fourth methyl group onto **12** (Scheme 3) proceeded with excellent *anti* selectivity (>99:1) to give **13a**. Remarkably, the use of CuBr/**4** resulted in epimer **13b** with identical excellent selectivity, which dem-



Scheme 3. a) MeMgBr, *ent*-**4**/CuBr (1 mol%), *t*BuOMe, −85°C, 18 h; 85%, *anti*/*syn* >99:1; b) MeMgBr, **4**/CuBr (1 mol%), *t*BuOMe, −85°C, 18 h; 88%, *syn*/*anti* >99:1.

onstrates the complete control of the catalyst in steering the chirality of the newly formed stereocentre. Such overwhelming catalyst control, overriding the strong natural preference of the substrate for *syn* addition, is unprecedented. As a consequence of the excellent stereoselectivities obtained throughout this part of the synthesis, the need for laborious separation of diastereomers is completely avoided.

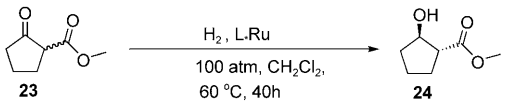
The conversion of **13a** into alcohol **15** (Scheme 4) was efficiently accomplished through an optimised Baeyer–Villiger oxidation and subsequent hydrolysis. Overall, **15** was prepared in 33% yield from **2**, which is a considerable improvement over the literature yields.[16,18] Protection of the hydroxy group as the THP ether, followed by deprotection of the TBDPS ether and TPAP oxidation of the formed alcohol, efficiently produced aldehyde **18**. A Reformatsky-type



Scheme 4. a) *m*-CPBA, $CHCl_3$, 60°C, 12 h, and repetition of the procedure on the recovered starting material; overall yield 85%; b) K_2CO_3, MeOH, RT, 3 h; 97%; c) dihydropyrane, PPTS, RT, 4 h; 98%; d) TBAF, THF, 5 h; 96%; e) TPAP, NMO, 4 Å MS, 1 h; 88%; f) 4-methoxybenzyl 2-bromoacetate, SmI_2, 30 min; 90%; g) TPAP, NMO, 4 Å MS, 1 h; 85%; h) (*R*)-[(RuCl(Tol-BINAP))$_2$(μ-Cl)$_3$[NH_2Me_2] (1 mol%), 5 bar H_2, EtOH, 8 h; 90%, *de* >99%; i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 1 h; j) LiOH, 4 h; 85% over 2 steps. (For compounds **4**, **5**, **8**, **14**, **16**, **17**, **19** and **22**, see the Supporting Information.) *m*-CPBA: *meta*-chloroperoxybenzoic acid; MS: molecular sieves; NMO: 4-methylmorpholine *N*-oxide; PMB: *para*-methoxybenzyl; PPTS: pyridinium *para*-toluenesulfonate; TBAF: tetrabutylammonium fluoride; Tf: trifluoromethanesulfonyl; Tol-BINAP: 2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl; TPAP: tetrapropylammonium perruthenate.

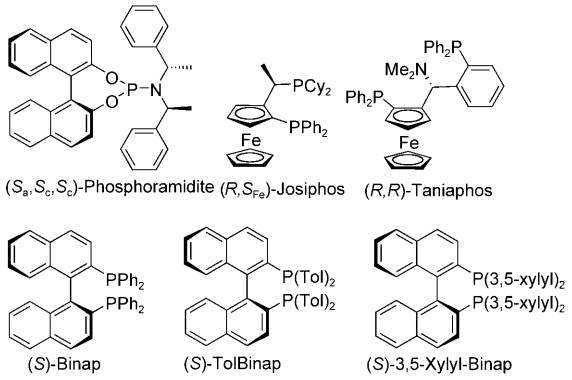
reaction of **18** mediated by SmI_2, followed by oxidation of the resulting hydroxy ester, afforded the corresponding β-ketoester **20**. Gratifyingly, catalytic asymmetric hydrogenation of **20** with 1 mol% (*R*)-[(RuCl(Tol-BINAP))$_2$(μ-Cl)$_3$-[NH_2Me_2][23] afforded **21** in 90% yield, with an excellent *de* value of >99%. Protection of **21** with TBSOTf, followed by basic hydrolysis resulted in **A**.

In connection with the synthesis of **B**, we started with a careful study of the asymmetric hydrogenation of **23** (Scheme 5). This asymmetric hydrogenation, with [$RuCl_2$(*p*-



Scheme 5. Asymmetric hydrogenation of cyclic β-ketoester **23**.

cymene)]$_2$ and BINAP as the chiral ligand, had been reported by Noyori et al.[24] to give **24** in 98% yield, 92% *ee* and an *anti*/*syn* ratio of 99:1. Further catalyst optimisation by variation of the ligand (Scheme 6) initially failed; the depict-



Scheme 6. Ligands used in the asymmetric hydrogenation. Tol: tolyl.

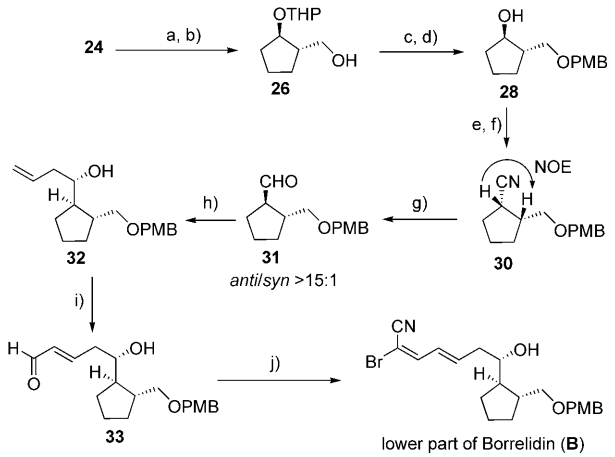
ed (S_a,S_c,S_c)-phosphoramidite, Josiphos and Taniaphos all gave incomplete conversion (Table 1). Tol-BINAP and xylyl-BINAP in combination with DPEN and DAIEPN, however, gave significant improvements in the *ee* and d.r. values. Finally, it turned out that, by applying 3,5-xylyl-BINAP as the chiral ligand in combination with [RuI_2(*p*-cymene)]$_2$ as the metal precursor, the outcome could be improved to an excellent 98% yield, 97% *ee* and an *anti*/*syn* ratio of >99:1. This strategy is very attractive for natural product synthesis because it provides excellent selectivities and is easily scalable to multigram quantities.

Further reduction of **24** to primary alcohol **26** (Scheme 7) was efficiently accomplished by THP protection of the secondary alcohol and reduction of the ester functionality. Primary alcohol **26** was PMB protected; this was followed by deprotection of the secondary alcohol to give **28**, which underwent subsequent tosylation and substitution with cyanide to result in **30.** The vicinal stereochemistry of the substitu-

Table 1. Catalyst optimisation for asymmetric hydrogenation of **23**.[a]

Ligand	Ruthenium source	Yield [%]	d.r.	*ee* [%]
BINAP	$[RuCl_2(p\text{-cymene})]_2$	95	96:4	90
phosphoramidite	$[RuCl_2(p\text{-cymene})]_2$	10	–	–
Josiphos	$[RuCl_2(p\text{-cymene})]_2$	30	–	–
Taniaphos	$[RuCl_2(p\text{-cymene})]_2$	25	–	–
L1	$[RuCl_2(p\text{-cymene})]_2$	90	97:3	94
L2	$[RuCl_2(p\text{-cymene})]_2$	95	97:3	95
Tol-BINAP	$[RuCl_2(p\text{-cymene})]_2$	96	98:2	94
3,5-xylyl-BINAP	$[RuCl_2(p\text{-cymene})]_2$	98	99:1	96
Tol-BINAP	$[RuI_2(p\text{-cymene})]_2$	97	99:1	95
3,5-xylyl-BINAP	$[RuI_2(p\text{-cymene})]_2$	98	99:1	97

[a] Optimised reaction conditions: (*R*)-3,5-xylyl-BINAP (0.6 mol%), $[RuI_2(p\text{-cymene})]_2$ (0.25 mol%), 100 bar H_2, CH_2Cl_2, 48 h; 98% yield, *anti*/*syn* 99:1, 97% *ee*. **L1**: (*R*)-3,5-xylyl-BINAP[(*R*)-DPEN]; **L2**: (*R*)-3,5-xylyl-BINAP[(*R*)-DAIPEN]. DPEN: 1,2-diphenyl-1,2-diaminoethane; DAIPEN: 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine.

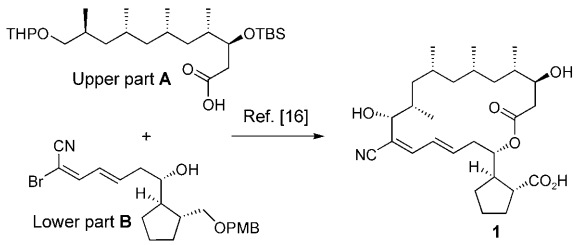


Scheme 7. a) Dihydropyrane, PPTS, RT, 4 h; 96%; b) $LiAlH_4$, THF, RT, 10 h; 93%; c) PMBCl, NaH, DMF, −20°C, 1 h; 95%; d) PPTS, EtOH, 50°C, 12 h; 96%; e) TsCl, pyridine, RT, 12 h; 98%; f) NaCN, DMSO, 50°C, 12 h; 80%; g) DIBALH, CH_2Cl_2, −65°C, 4 h; 85%; h) allyltrimethylsilane, $MgBr_2{\cdot}Et_2O$; 86%; i) Hoveyda–Grubbs second-generation catalyst (5.0 mol%), acrolein diethylacetal, CH_2Cl_2, 45°C, 18 h; acidic work up; 75%; j) $(EtO)_2P(O)CH(Br)CN$, DBU, LiCl, 0°C, 4 h; 93%. (For compounds **25**, **27** and **29**, see the Supporting Information.) DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF: *N*,*N*-dimethylformamide; DMSO: dimethylsulfoxide; Ts: toluene-4-sulfonyl.

ents in **30** was confirmed to be *cis*, as expected, by ^{1}H-NOE experiments (see the Supporting Information). Reduction of *syn*-**30** with DIBALH, followed by aqueous work up, led selectively to the desired *anti*-aldehyde **31** (*anti*/*syn* > 15:1) in 85% yield. This in situ epimerisation leading to the required *anti* compound was hoped for and, indeed, takes place readily under the reaction conditions.

Chelation-controlled allylation of **31** (Scheme 7) with allyltrimethylsilane catalysed by the Lewis acid $MgBr_2{\cdot}Et_2O$ afforded homoallylic alcohol **32** with high yield and excellent stereoselectivity (*anti*/*syn* 20:1), as reported by Omura et al.[16] From compound **32**, we envisioned that the use of olefin metathesis could drastically shorten the existing routes to **B** and even avoid protection of the secondary alcohol. Direct installation of the cyanodiene unit stereoselectively by this approach turned out to be impossible. Invariably, *Z*,*E* mixtures were obtained. As the cross-metathesis of unprotected homoallylic alcohols with methyl acrylate has been documented, we decided to use this as a starting point. We were very pleased to see that cross-metathesis of homoallylic alcohol **32** with acrolein diethylacetal[25] and a Hoveyda–Grubbs second-generation catalyst, followed by careful acidic workup, efficiently produced *E*-**33** as the only isomer in 75% yield after isolation. Subsequent HWE olefination of **33** with $(EtO)_2P(O)CH(Br)CN$[26] completed the synthesis of fragment **B**. This concise "catalytic synthesis" of **B** affords a considerably higher overall yield than the reported routes and is readily scaled up.

The characterisation data of **A** and **B** thus synthesised are in excellent agreement with those reported in the literature. The remainder of the synthesis (Scheme 8) can be carried out as described by Omura et al.[16]



Scheme 8. Final steps in the synthesis of borrelidin (**1**).

Conclusion

In conclusion, we have completed an efficient formal total synthesis of borrelidin (**1**). This synthesis is significantly shorter and produces **1** in much higher yield than previously reported. The present approach makes maximum benefit of asymmetric catalysis, in particular, the copper-catalysed asymmetric conjugate addition of methylmagnesium bromide and the ruthenium-catalysed asymmetric ketone hydrogenation. Due to the excellent stereoselectivities, separation of diastereomers is obsolete. This catalytic approach paves the way for the preparation of borrelidin analogues, particularly stereoisomers in addition to modifications of the carbon skeleton, and further research will be focused in this direction.

Experimental Section

General: All reactions were carried out under a nitrogen atmosphere with dried glassware. All solvents were dried and distilled before use according to standard procedures. All reagents were commercially obtained (Aldrich, Acros) at the highest commercial quality and used without further purification, except where noted. Chromatography was performed with Merck silica gel type 9385, 230–400 mesh; TLC was performed with Merck silica gel 60, 0.25 mm. Components were visualised by staining with Seebach's reagent, a mixture of phosphomolybdic acid (25 g), cerium(IV) sulfate (7.5 g), H_2O (500 mL) and H_2SO_4 (25 mL). High-resolu-

tion mass spectra (HRMS) were recorded on a AEI-MS-902 and FTMS orbitrap (Thermo Fisher Scientific) mass spectrometer. ^{1}H, ^{13}C and APT spectra were recorded on a Varian AMX400 spectrometers (400 and 100.59 MHz, respectively) with $CDCl_3$ as the solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: $\delta = 7.26$ ppm for ^{1}H, $\delta = 77.23$ ppm for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; br: broad; m: multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a Schmidt and Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g per 100 mL). Enantiomeric excesses were determined by HPLC (Chiralcel OB (250×4.6, 10 μm) or Chiralcel OD (250×4.6, 10 μm) column) and capillary GC analysis (Chiraldex A-TA (30 m×0.25 mm) column) with a flame-ionisation detector and by comparison with racemic products.

1,4-Addition on α,β-unsaturated thioesters (15 g scale): Synthesis of compound 3: (R,S_{Fe})-Josiphos (**4**)·CuBr complex (290 mg, 0.39 mmol, 1 mol%) was dissolved in *t*BuOMe (214 mL) under nitrogen. The solution was cooled to −85 °C and methylmagnesium bromide (15.6 mL, 46.8 mmol, solution in diethyl ether) was added dropwise over 20 min. After the reaction mixture had been stirred for 20 min, a solution of thioester **2** (15 g, 39.0 mmol) in *t*BuOMe (64 mL) was added with a syringe pump over 2 h. The reaction mixture was stirred at −85 °C for 22 h, then quenched by addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH_4Cl was added, and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (eluent: pentane/diethyl ether, 40:1) to afford **3** as a colourless oil (95% yield, 98% *ee*). The enantiomeric excess was determined by HPLC (Chiralcel OB, 250×4.6, 10 μm; eluent: heptane/IPA 95:5; 23.38 min (major), 28.78 min (minor)) to be 98% *ee* or by GC analysis (Chiraldex AT-A, 30.0 m×0.25 mm; 1.0 mL min^{-1}; initial temperature: 50 °C, then 5 °C min^{-1} to a final temperature of 170 °C; 19.5 min (major), 19.7 (minor)) to be 98% *ee*; $[\alpha]_D^{25} = -8.5$ ($c = 1.7$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.66$ (dd, $J = 6.8$, 1.4 Hz, 4H), 7.47–7.35 (m, 6H), 3.54 (dd, $J = 10.0$, 5.3 Hz, 1H), 3.46 (dd, $J = 9.9$, 6.3 Hz, 1H), 2.88 (q, $J = 7.4$ Hz, 2H), 2.83 (dd, $J = 14.5$, 5.3 Hz, 1H), 2.38 (dd, $J = 14.5$, 8.4 Hz, 1H), 2.28 (m, 1H), 1.25 (t, $J = 7.4$ Hz, 3H), 1.15 (s, 9H), 0.97 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 199.2$ (s), 135.62 (d), 133.63 (s), 129.58 (d), 127.50 (d), 67.90 (t), 47.75 (t), 33.76 (d), 26.84 (q), 23.27 (t), 19.28 (s), 16.40 (q), 14.86 ppm (q); HRMS: calcd for $C_{19}H_{23}O_2SSi$ [M−*tert*-butyl]: 343.1188; found: 343.1183.

1,4-Addition on α,β-unsaturated ketones: Synthesis of compound 13a: (R,S_{Fe})-Josiphos (**4**)·CuBr complex (18.5 mg, 0.0249 mmol, 1 mol%) was dissolved in *t*BuOMe (5 mL) under nitrogen. The mixture was cooled to −80 °C and methylmagnesium bromide (0.996 mL 2.44 mmol, solution in diethyl ether) was added dropwise over 10 min. After the reaction mixture had been stirred for 10 min, a solution of thioester **12** (1.2 g, 2.49 mmol) in *t*BuOMe (7.2 mL) was added with a syringe pump over 1.5 h. The reaction mixture was stirred at −80 °C for 18 h, then quenched by the addition of MeOH and allowed to warm to room temperature. Saturated aqueous NH_4Cl was added, and after phase separation and extraction of the aqueous phase with diethyl ether, the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (eluent: pentane/diethyl ether, 40:1) to afford **13a** as a colourless oil (1.01 g, 85% yield): *anti*/*syn* ratio determined by NMR spectroscopy: >99:1; $[\alpha]_D^{25} = -19.4$ ($c = 1.39$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (d, $J = 7.1$ Hz, 4H), 7.39 (dd, $J =$ 15.8, 8.6 Hz, 6H), 3.54–3.38 (m, 2H), 2.28 (dt, $J = 23.4$, 12.6 Hz, 2H), 2.11 (s, 3H), 1.72 (dd, $J = 12.6$, 5.9 Hz, 1H), 1.54 (dd, $J = 14.5$, 8.8 Hz, 3H), 1.34 (dt, $J = 13.1$, 6.5 Hz, 1H), 1.05 (d, $J = 0.5$ Hz, 9H), 0.86 ppm (ddd, $J = 27.2$, 13.6, 6.5 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 208.93$, 135.76, 134.22, 129.64, 127.72, 68.94, 52.44, 46.19, 44.10, 41.61, 33.27, 30.58, 27.57, 27.35, 27.07, 26.85, 20.78, 20.38, 19.43, 18.25 ppm; HRMS: calcd for $C_{31}H_{48}O_2Si$ [M+Na^+]: 503.3321; found: 503.3315.

Catalytic asymmetric hydrogenation of β-ketoesters: Synthesis of compound 21: A solution of **20** (152 mg, 0.32 mmol) and (*R*)-[(RuCl(Tol-BINAP))$_2$(μ-Cl)$_3$[NH_2Me_2] (5.7 mg, 0.0032 mmol) in EtOH (3 mL) was placed in an autoclave and purged with N_2 and H_2. Hydrogen was introduced (5 bar) and the reaction mixture was stirred at room temperature for 8 h. After the hydrogen pressure was released, the solution was concentrated under reduced pressure and purified by flash chromatography (eluent: pentane/EtOAc, 50:10) to afford **21** (137 mg, 90%, *anti*/*syn* >99:1). The diastereomeric ratio of **21** was determined by NMR spectroscopy by comparison with the spectra of the diastereomers prepared by reduction of β-ketoester **20** with $NaBH_4$; $[\alpha]_D^{25} = -19.2$ ($c = 0.75$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (s, 2H), 6.90 (s, 2H), 5.09 (s, 2H), 4.58 (s, 1H), 3.94 (s, 1H), 3.81 (s, 5H), 3.53 (d, $J = 25.0$ Hz, 2H), 3.17 (d, $J = 36.2$ Hz, 1H), 2.70 (s, 1H), 2.48 (ddd, $J = 19.3$, 16.3, 6.3 Hz, 3H), 1.82 (s, 3H), 1.60 (s, 8H), 1.25 (s, 3H), 0.88 ppm (s, 16H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 173.60$, 159.91, 130.39, 127.92, 114.19, 99.28, 98.88, 74.18, 73.95, 70.72, 66.58, 62.52, 62.27, 55.50, 45.76, 41.08, 40.54, 39.33, 35.25, 30.98, 29.91, 27.38, 25.75, 20.99, 20.60, 19.87, 17.00, 14.70 ppm; HRMS: calcd for $C_{28}H_{46}O_6$ [M+Na^+]: 501.3192; found: 501.3186.

Catalytic asymmetric hydrogenation of cyclic β-ketoesters: Synthesis of compound 24: A solution of **23** (5.0 g, 35.19 mmol), (*R*)-3,5-xylyl-BINAP (155 mg, 0.211 mmol) and $[RuI_2(p\text{-cymene})]_2$ (86 mg, 0.087 mmol) in CH_2Cl_2 was placed in an autoclave and purged with N_2 and H_2. Hydrogen was introduced (100 bar) and the reaction mixture was stirred at 60 °C for 48 h. After the hydrogen pressure was released, the solution was concentrated under reduced pressure and purified by flash chromatography (eluent: pentane/EtOAc, 1:1) to afford (1*R*, 2*R*)-**24** (4.99 g, 98%); *anti*/*syn* ratio determined by NMR spectroscopy: 99:1; enantiomeric excess and absolute configuration determined by HPLC (Chiralcel OD, 250× 4.6, 10 μm; eluent: heptane/IPA, 99:1; 23.883 min (major), 29.856 min (minor)): 97% *ee*; $[\alpha]_D^{25} = -49.8$ ($c = 2.51$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.36$ (q, $J = 6.5$ Hz, 1H), 3.80–3.61 (m, 3H), 2.76–2.62 (m, 1H), 2.19 (s, 1H), 2.12–1.91 (m, 2H), 1.89–1.54 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 175.75$, 75.92, 52.46, 51.53, 34.18, 27.52, 22.19 ppm; HRMS: calcd for $C_7H_{12}O_3$ [M−H^-]: 143.0786; found: 143.0702.

Synthesis of compound 31: DIBALH (4.46 mL, 4.46 mmol, 1.0 M solution in CH_2Cl_2) was added to a stirred mixture of **30** (500 mg, 2.03 mmol) in CH_2Cl_2 (30 mL) at −65 °C under nitrogen. Stirring was continued until the reduction was completed (3–4 h). The reaction mixture was quenched with saturated aqueous Rochelle salt (potassium sodium tartrate; 30 mL) and stirred for 30 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to yield crude aldehyde **31** as a colourless oil (428 mg, 85% yield). The spectral data of **31** were consistent with those reported in the literature:[16a,b] $[\alpha]_D^{25} = -25.8$ ($c = 0.29$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.65$ (d, $J = 2.6$ Hz, 1H), 7.25–7.22 (m, 2H), 6.89–6.85 (m, 2H), 4.44 (d, $J = 1.6$ Hz, 2H), 3.81–3.79 (m, 3H), 3.46 (dd, $J = 9.1$, 5.8 Hz, 1H), 3.33 (dd, $J = 9.1$, 7.4 Hz, 1H), 2.58–2.43 (m, 2H), 1.83 (ddt, $J = 12.7$, 6.6, 5.6 Hz, 4H), 1.70–1.58 (m, 2H), 1.38 ppm (dd, $J = 12.5$, 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 204.02$, 159.33, 130.71, 129.31, 113.96, 73.18, 72.89, 56.00, 55.48, 41.43, 29.59, 26.79, 25.19 ppm; HRMS: calcd for $C_{15}H_{20}O_3$ [M+Na^+]: 271.1310; found: 271.1295.

Synthesis of B through olefin cross-metathesis and HWE reaction: A flame-dried Schlenk flask under a nitrogen atmosphere was charged with **32** (520 mg, 1.79 mmol), acrolein diethylacetal (820 μL, 5.37 mmol) and CH_2Cl_2 (8.5 mL). Hoveyda–Grubbs second-generation catalyst (56 mg, 0.089 mmol) was added and the resulting solution was stirred for 18 h with heating to reflux. The reaction was then quenched with water (5 mL) and formic acid (0.4 mL) and stirred for 1 h. After phase separation and extraction of the aqueous phase with CH_2Cl_2, the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (eluent: pentane/EtOAc, 40:8) to afford **33** as a colourless oil (427 mg, 75% yield, only the *E* isomer observed). DBU (143 mg, 0.94 mmol) and lithium chloride (40 mg, 0.94 mol) were added to a stirred mixture of **33** (150.5 mg, 0.47 mmol) and $(EtO)_2P(O)CH(Br)CN$ (360 mg, 1.41 mmol)[5] in MeCN (5 mL) at 0 °C. The solution was stirred for 4 h, then quenched with saturated aqueous $NaHCO_3$, and after phase separation and extraction of the aqueous phase with EtOAc, the combined organic phases were dried

over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (eluent: pentane/EtOAc, 40:8) to afford **B** as a colourless oil (183 mg, 93% yield, *E*/*Z* 95/5). The spectral data of **B** were consistent with those reported in the literature:[16a,b] $[\alpha]_D^{25} = +11.1$ ($c = 0.24$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7.22 (m, 2H), 7.17–7.14 (m, 1H), 6.90–6.86 (m, 2H), 6.41 (dd, $J = 7.7$, 5.5 Hz, 2H), 4.78 (d, $J = 6.2$ Hz, 1H), 4.50 (t, $J = 7.3$ Hz, 2H), 3.84–3.78 (m, 3H), 3.56 (dd, $J = 8.7$, 3.9 Hz, 1H), 3.41 (dd, $J = 11.4$, 4.0 Hz, 1H), 3.14 (dd, $J = 10.7$, 8.8 Hz, 1H), 2.53–2.43 (m, 1H), 2.23 (dd, $J = 14.5$, 7.2 Hz, 1H), 2.04 (dd, $J = 9.0$, 7.0 Hz, 1H), 1.77 (ddd, $J = 12.4$, 9.4, 7.5 Hz, 2H), 1.64–1.46 (m, 3H), 1.31–1.18 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 159.48$, 150.28, 144.52, 129.61, 129.32, 127.38, 114.89, 113.99, 84.08, 74.80, 74.22, 73.11, 55.37, 52.51, 44.31, 39.91, 31.22, 29.90, 24.54 ppm; HRMS: calcd for $C_{21}H_{26}BrNO_3$ [$M-H^+$]: 418.1096; found: 418.0998.

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