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Enantioselective biocatalytic reduction of 2,2-disubstituted ethylacetoacetates: an indirect desymmetrization approach for the synthesis of enantiopure (*S*)-4-hydroxy-3,3-disubstituted pentane-2-ones

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ABSTRACT

Ethyl 2,2-disubstituted-3-oxobutanoates were biocatalytically reduced to the corresponding (*S*)-ethyl 3-hydroxy-2,2-disubstitutedbutanoate with the growing cells of *Klebsiella pneumoniae* (NBRC 3319) with excellent enantioselection. The biocatalytically derived enantiopure hydroxyl esters were then synthetically manipulated to give (*S*)-4-hydroxy-3,3-disubstituted pentane-2-ones. The whole process can be regarded as an indirect enantioselective enzymatic desymmetrization method for the synthesis of (*S*)-4-hydroxy-3,3-disubstituted pentane-2-ones.

1. Introduction

The desymmetrization or off-mirror plane reaction of σ-symmetric organic compounds always leads to one or more unsymmetrical products (mainly enantiomers).[1] This synthetic operation can be considered as a very useful functional group interconversion and should be taken into serious consideration when performing retrosynthetic analyses. It is always more convenient to start with symmetrical intermediates with a σ-plane and perform the desymmetrization to further the synthetic progression.[2] Enantioselective enzymatic desymmetrizations are reactions in which a meso/prochiral small organic molecules with a σ plane can be enantioselectively desymmetrized with the help of an enzyme (enatiotopos/enantioface differentiating reaction) to yield a single enantiomer in theoretically 100% yield.[3] The stereoselective bioreduction of prochiral ketones for the synthesis of chiral secondary alcohols using plant and microbial ketoreductases has been well explored over the last two decades.[4] β-Keto esters (simple and α-substituted) are usually known as excellent substrates for several ketoreductases (plant, microbial, recombinant) for the asymmetric synthesis of the corresponding β-hydroxyesters.[5] Enantiopure β-hydroxy esters are useful precursors for the synthesis of various small organic molecules and are regarded as well explored chiral pool material by their own merit. Very recently, we reported that the fermenting cells of *Klebsiella pneumoniae* can (NBRC 3319) act as a versatile ketoreductase and selectively reduce several α-substituted β-keto esters through a unique dynamic kinetic resolution pathway to yield the corresponding *syn*-β-hydroxy esters with remarkable stereocontrol (de >99%, ee >99%). We have also explored the synthetic potential of enantiopure α-substituted-β-hydroxy esters for accessing a series of small carbocycles and heterocycles.[6]

Over the course of our studies, we were interested in exploring the substrate scope of *Klebsiella pneumoniae* (NBRC 3319) and we found that it accepts several α-substitutions (alkyl, allyl, benzyl and propargyl) in the parent β-keto ester moiety as its substrate and that it yields the respective hydroxyl esters in excellent yield. It was also observed that the fermenting cells of *Klebsiella pneumoniae* (NBRC 3319) accept α-substituted acetoacetate (bearing a terminal –Me group) as its main substrate. 3-Substituted (mono- and di-)pentane-2,4-dione (substituted acetylacetones) was not accepted by the enzyme as its substrate, hence direct enantioselective enzymatic desymmetrizations of pro-chiral acetylacetones were not possible by the enzyme system (probable enantioselective enzymatic desymmetrization routes are outlined in Scheme 1). We argued that if the 2,2-disubstituted ethylacetoacetate analogue can undergo enantioselective bioreduction with *K. pneumoniae*, then it is possible to synthetically manipulate the obtained β-hydroxy keto esters to (*S*)-4-hydroxy-3,3-dialkylpentane-2-ones (Scheme 1). Hence an indirect enantioselective enzymatic desymmetrization route can be explored efficiently since a direct enantioselective enzymatic desymmetrization route seems to not work with the given enzyme system. In addition there are very

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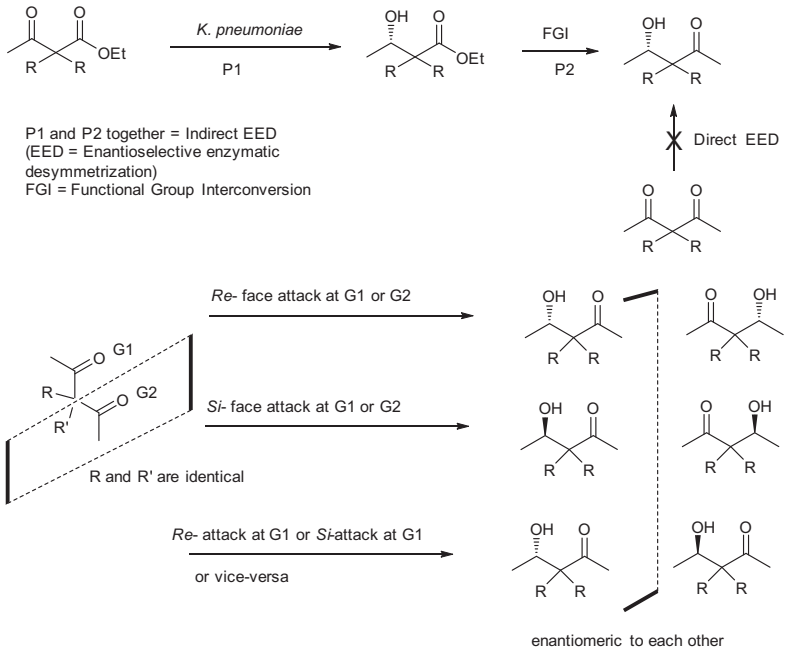


Scheme 1. Direct and indirect enantioselective enzymatic desymmetrization route to 3,3-disubstituted acetylacetones and limitations to the direct desymmetrization method.

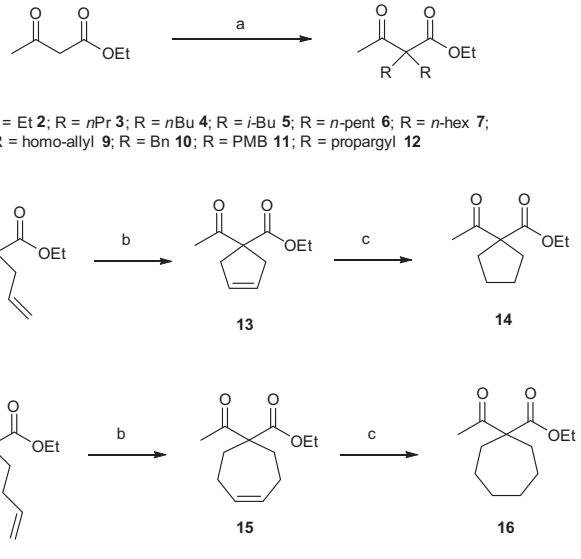
few reports for the enantiopure synthesis of (*S*)-4-hydroxy-3,3-dialkylpentane-2-ones in the literature.[7] This finding also prompted us to investigate an efficient enantioselective synthesis for those compounds, which might act as valuable chiral intermediates in the field of asymmetric synthesis.

2. Results and discussion

Initially we wondered if 2,2-symmetrically di-substituted ethylacetoacetates could undergo enantioselective bioreduction with the fermenting whole cells of *Klebsiella pneumoniae* (NBRC 3319), then it would be easier for us to explore the indirect enantioselective enzymatic desymmetrization strategy as outlined in Scheme 1. The process seems to be very challenging and interesting as there is no literature precedence for the enantioselective bioreduction of 2,2-symmetrically di-substituted ethylacetoacetates. This bioreduction system involving 2-substituted (mono) ethyl acetoacetates follows a unique dynamic kinetic resolution (dynamic kinetic resolution) pathway due to the presence of an epimerizable α-hydrogen and excellent enantio- and diastereocontrol was observed in the product β-hydroxyesters. Conversely, the bioreduction of 2,2-symmetrically di-substituted ethylacetoacetates has to follow a normal pathway (due to the lack of an α-hydrogen at the 2-position) and can only lead to two enantiomeric products.

We synthesized several 2,2-symmetrically di-substituted ethylacetoacetates starting from ethyl acetoacetate. The synthesis involves standard base mediated anion generation at the α-carbon followed by quenching with 2 equiv of the electrophiles (alkyl halides) as shown in Scheme 2.

The synthesis of compounds **1**–**12** was straightforward and carried out as depicted in Scheme 2. We also synthesized 2,2-symmetrically substituted cyclic ethyl acetoacetates **13**–**16**. For this purpose, compounds **8** and **9** were used as starting materials. Ring closing metathesis reaction with Grubbs first generation catalyst (G-I)[8] at room temperature afforded the corresponding



Scheme 2. Synthesis of 2,2-symmetrically di-substituted ethylacetoacetates. Reagents and conditions: (a) NaH, alkyl halides, THF, rt to reflux, 68–92%; (b) G–I (5 mol %), DCM, rt, 80%; (c) Pd–C/H_2, MeOH, rt, 95%.

cyclic compounds **13** and **15**. Compounds **13** and **15** upon hydrogenation on Pd/C furnished compounds **14** and **16** in excellent yield.

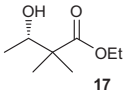
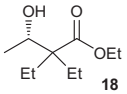
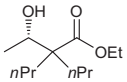
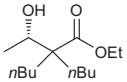
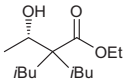
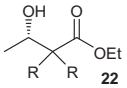
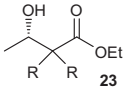
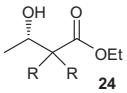
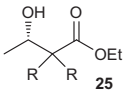
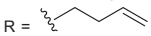
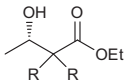
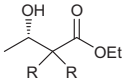
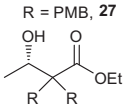
2.1. Bioreduction of compounds 1–16

The simplest substrate ethyl 2,2-dimethyl-3-oxobutanoate **1** (100 mg; 0.63 mmol) was directly added to the growing cells of *Klebsiella pneumoniae* (NBRC 3319). The reactions were monitored periodically by TLC analysis. It usually required 7–10 days for

quantitative conversion, after which the product alcohol was extracted with EtOAc and purified by standard techniques. The reduced alcohol was obtained in 85% yield with excellent enantioselection (ee >99%; as determined by chiral HPLC analysis of the corresponding benzoate derivative). The remaining substrates were then subjected to bioreduction with the growing cells of *Klebsiella pneumoniae* and the results are shown in Table 1.

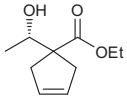
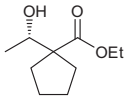
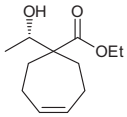
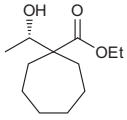
From Table 1 it is evident that a structurally diverse set of substrates are accepted by the whole cell of *K. pneumoniae* and the corresponding β-hydroxyesters are obtained with excellent enantioselection. Although the bioreduction usually took a long time (7–10 days) for the complete consumption of the starting material, it is worth mentioning that excellent enantioselection (>99%) was observed in all the cases.

Table 1
Enantioselective bioreduction of compounds **1**–**16** with *K. pneumoniae*

Entry (compound)	Product[a]	Time required (days), conversion[b] (%)	ee[c] (%)
1	 **17**	7, 85	>99
2	 **18**	7, 82	>99
3	 **19**	7, 80	>99
4	 **20**	8, 68	>99
5	 **21**	7, 70	>99
6	 **22** R = nC_5H_{11}	9, 65	>99
7	 **23** R = nC_6H_{13}	10, 65	>99
8	 **24** R = allyl	7, 88	>99
9	 **25** R = 	7, 85	>99
10	 R = $-CH_2Ph$, **26**	8, 68	>99
11	 R = PMB, **27**		>99
12	 R = propargyl, **28**	8, 72	>99

(*continued on next page*)

Table 1 (*continued*)

Entry (compound)	Product[a]	Time required (days), conversion[b] (%)	ee[c] (%)
13	 **29**	8, 70	>99
14	 **30**	8, 76	>99
15	 **31**	9, 70	>99
16	 **32**	9, 72	>99

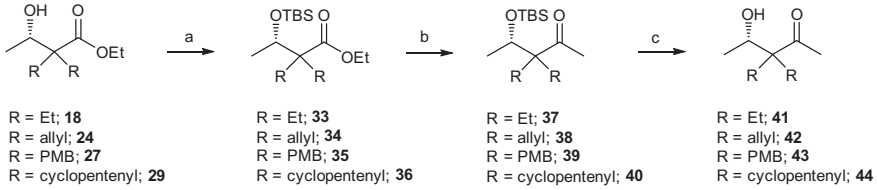
[a] The synthesized alcohols have an (*S*)-configuration.
[b] The % of conversion was measured after isolation and purification of the product.
[c] Measured by chiral HPLC (Chiralpak IC) of the corresponding benzoate derivative.

2.2. Indirect desymmetrization of biocatalytically derived enantiopure hydroxyesters

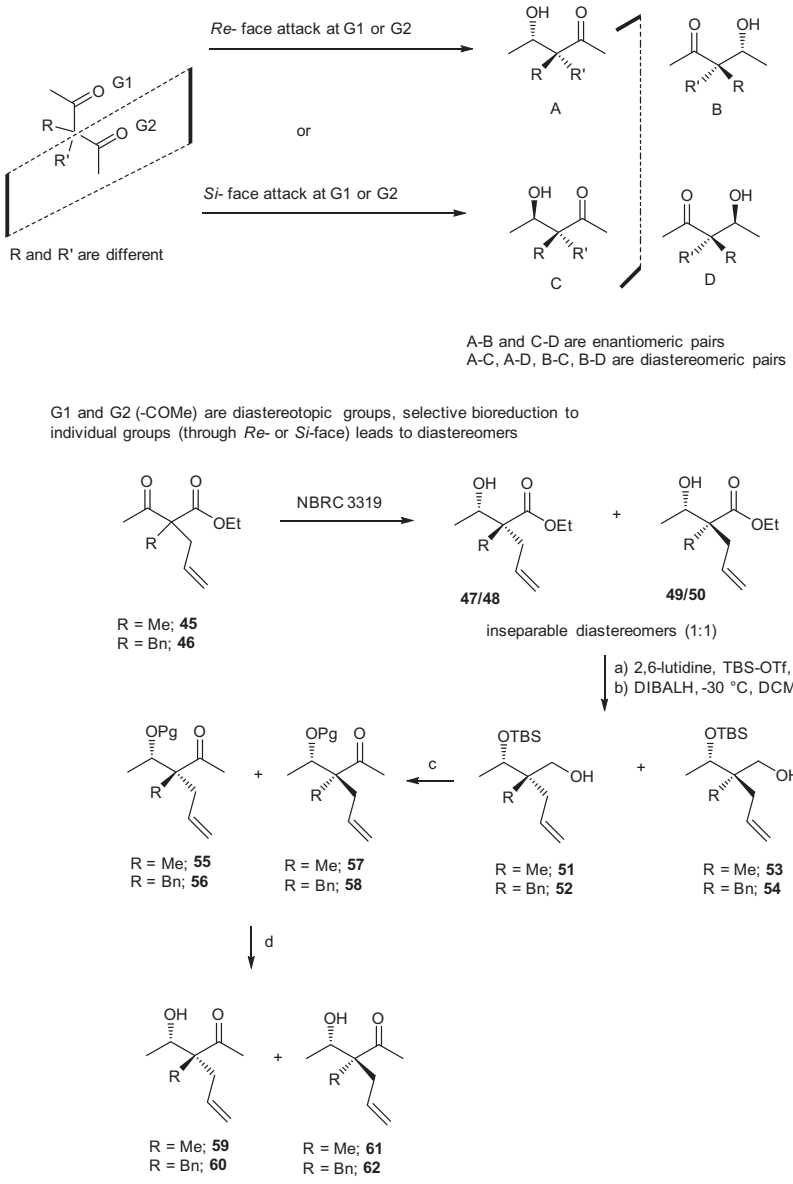
After the initial synthesis of the chiral hydroxy esters was achieved through bioreduction with the whole cell of *K. pneumoniae*, we turned our attention to the indirect desymmetrization method as depicted earlier. For this purpose, the free hydroxyl group was protected as its TBS ether by treatment with TBS-OTf in the presence of 2,6-lutidine[9] to afford the corresponding silylated esters **33**–**36** in good yield. The esters were then converted into the corresponding Weinreb amides by treatment with *N*,*O*-dimethylhydroxylamine in the presence of $AlMe_3$ with good yield.[10] The crude Weinreb amides was then subjected to reaction with MeMgI at 0 °C to afford the corresponding methyl ketones **37**–**40** as shown in Scheme 3. The TBS group was then deprotected by using pyridinium *p*-toluenesulfonate in MeOH to afford compounds **41**–**44** (the desymmetrized products of the corresponding 3,3-dialkyl-pentane-2,4-diones). Hence, the overall reaction sequence can be regarded as an efficient indirect enantioselective enzymatic desymmetrization of the parent acetylacetones for the synthesis of enantiopure β-hydroxy ketones in good yield.

2.3. Indirect diastereoselective enzymatic desymmetrization of 3,3-unsymmetrically disubstituted acetyl acetones

The situation will become more complex if the parent acetyl acetone becomes unsymmetrically substituted with two different groups at the 3-position. Such a system is shown in Scheme 4. Here the two –COMe groups (G1 and G2) are not enantiotopic any more as shown in Scheme 1; due to the presence of a pro-chiral assembly (at C3) are diastereotopic under nucleophilic attack conditions at G1 or G2. In principle, two pathways can operate; in one kinetic resolution followed by selective bioreduction to the carbonyl functionality leads to only one stereoisomer (out of the four compounds). In the other pathway, selective bioreduction leads to two diastereomers with absolute enantiocontrol. The parent 3, 3-unsymmetric substituted acetyl acetones are not accepted by the whole cells of *K. pneumoniae*, hence we opted for the indirect desymmetrization route as depicted earlier. Ethyl 2-acetyl-2-methylpent-4-enoate **45** and ethyl 2-acetyl-2-benzylpent-4-enoate **46** were chosen as the starting substrates. The bioreduction of **45**/**46** with the growing cells of *K. pneumoniae* went smoothly and after 8 days of incubation, an inseparable mixture of the two diastereoisomers **47**/**49** and **48**/**50** were isolated (as indicated by ^1H and ^{13}C NMR analysis; 1:1 ratio) in 70% yield. The free secondary hydroxyl group was then protected as a TBS ether, and then subsequent reduction with DIBAL-H at −30 °C afforded the corresponding alcohols **51**/**53** and **52**/**54**, which were then separated by chromatography and spectroscopically well characterized. Functional group manipulation of **51**/**53** and **52**/**54** through a four step (oxidation, addition of MeMgI, oxidation and TBS group removal) procedure yielded enantiopure β-hydroxy acetylacetone derivatives **59**/**61** and **60**/**62** (the direct desymmetrized products obtained through a nucleophilic 'H' transfer to the parent acetyl acetone; Scheme 4).



Scheme 3. Indirect desymmetrization of biocatalytically derived 2,2-symmetrically substituted β-hydroxy esters; Reagents and conditions: (a) 2,6-lutidine, TBS-OTf, rt; (b) MeNH(OMe), $AlMe_3$, benzene, MeMgI, diethyl ether, 0 °C to rt; (c) pyridinium *p*-toluenesulfonate, MeOH, rt.



Scheme 4. Indirect diastereoselective enzymatic desymmetrization approach for the synthesis of enantiopure 3,3-dialkylated-4-hydroxy-pentan-2-ones. Reagents and conditions: (c) (i) BAIB, TEMPO, DCM, rt; (ii) MeMgI, Et_2O, 0 °C to rt; (iii) BAIB, TEMPO, DCM, rt; (d) pyridinium *p*-toluenesulfonate, MeOH, rt.

The absolute configuration of alcohols **59** and **61** was confirmed by comparing spectroscopic data with those of known compounds.[7c] From the above results it was clear that both enantiomers of racemic **45**/**46** react in a similar fashion and the bioreduction occurs from the *Re*-face of the carbonyl group in the same way as reported in the case of compounds **1**–**16**. It would have been more interesting if a kinetic resolution (fast reacting enantiomer of **45**/**46**) followed by carbonyl reduction by ketoreductase occurred, however both enantiomers of **45**/**46** were equally accepted by *K. pneumoniae* and yielded compounds **47**/**49** and **48**/**50** in equal amounts with excellent enantioselection.

3. Conclusion

In conclusion, ethyl 2,2-disubstituted-3-oxobutanoates were biocatalytically reduced to the corresponding (*S*)-ethyl 3-hydroxy-2,2-disubstitutedbutanoate with the growing cells of *Klebsiella pneumoniae* (NBRC 3319) with excellent enantioselection. The reported method serves as an indirect biocatalytic desymmetrization procedure for the synthesis of (*S*)-4-hydroxy-3,3-disubstituted pentane-2-ones. The synthesized enantiopure (*S*)-4-hydroxy-3,3-disubstituted pentane-2-ones could be used as excellent chiral precursors in asymmetric synthesis. Racemic ethyl 2,2-unsymmetrically disubstituted-3-oxobutanoates were also efficiently reduced to the corresponding enantiopure alcohols with excellent enantioselection. This type of enantioselective biocatalytic reduction with the growing cells of *Klebsiella pneumoniae* (NBRC 3319) is unique in the sense that there are few reports for the synthesis of such chiral β-hydroxyl-esters.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethylether were distilled from sodiumbenzophenone ketyl. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from CaH_2. Microbial ketoreductases strain form *Klebsiella pneumoniae* (NBRC 3319) was obtained from NBRC, Japan and

maintained in a Petri dish as well as in glycerol slants periodically. Bioreductions were performed in an incubator shaker at 35 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were acquired in $CDCl_3$ unless otherwise mentioned. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, δ = 0.00 ppm), and are referenced to residual solvent ($CDCl_3$, δ = 7.26 ppm (^{1}H) and 77.23 ppm (^{13}C). Coupling constants (J) are reported in Hertz (Hz) and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons. Optical rotations were measured on a JASCO P1020 digital polarimeter. Mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyser).

4.2. Synthesis of α,α-alkylacetoacetates 1–12: general procedure

At first, K_2CO_3 (2.712 g, 19.625 mmol) was added to a solution of ethylacetoacetate (1 mL, 7.85 mmol) in dry DMF (25 mL) at room temperature under an argon atmosphere, after which the corresponding alkyl halide (3 equiv) and (nBu)$_4$NI (319 mg, 0.8635 mmol) were added to the mixture and stirred at reflux. After 12 h the reaction mixture was cooled to room temperature and then water was added to quench the reaction and extracted with Et_2O (50 mL × 3). The combined organic layers were washed with H_2O (2 × 30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by flash chromatography (SiO_2, EtOAc/hexane).

4.2.1. Ethyl 2,2-dimethyl-3-oxobutanoate 1

R_f = 0.5 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.08 (q, J = 7.2 Hz, 2H), 2.05 (s, 3H), 1.25 (s, 6H), 1.15 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.8, 173.5, 61.3, 55.7, 25.7, 21.8, 14.0. HRMS (ESI) for $C_8H_{14}O_3Na$ [M+H]$^+$ calculated: 181.0841, found: 181.0848.

4.2.2. Ethyl 2,2-diethyl-3-oxobutanoate 2

R_f = 0.6 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.23–4.05 (m, 2H), 2.09 (s, 3H), 1.98–1.77 (m, 4H), 1.27–1.20 (m, 3H), 0.74 (t, J = 7.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.5, 172.7, 64.3, 61.1, 26.8, 23.6, 14.2, 8.2. HRMS (ESI) for $C_{10}H_{18}O_3Na$ [M+H]$^+$ calculated: 209.1154, found: 209.1159.

4.2.3. Ethyl 2-acetyl-2-propylpentanoate 3

R_f = 0.7 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.19–4.00 (m, 2H), 2.06 (s, 3H), 1.82–1.63 (m, 4H), 1.25 (t, J = 1.6 Hz, 3H), 1.21–1.11 (m, 10H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.4, 172.7, 63.5, 61.0, 33.5, 26.6, 17.2, 14.5, 14.1. HRMS (ESI) for $C_{12}H_{22}O_3Na$ [M+H]$^+$ calculated: 237.1467, found: 237.1474.

4.2.4. Ethyl 2-acetyl-2-butylhexanoate 4

R_f = 0.7 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.17 (q, J = 7.2 Hz, 2H), 2.09 (s, 3H), 1.87–1.77 (m, 4H), 1.36–1.20 (m, 7H), 1.10–1.02 (m, 4H), 1.00–0.84 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.8, 172.9, 63.6, 61.2, 31.0, 26.8, 26.1, 23.2, 14.3, 14.0. HRMS (ESI) for $C_{14}H_{26}O_3Na$ [M+H]$^+$ calculated: 265.1780, found: 265.1789.

4.2.5. Ethyl 2-acetyl-2-isobutyl-4-methylpentanoate 5

R_f = 0.4 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.13 (q, J = 7.2 Hz, 2H), 2.12 (s, 3H), 1.92–1.76 (m, 4H), 1.58–1.45 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 0.89–0.81 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 206.2, 173.4, 62.7, 61.1, 40.3, 26.8, 24.2, 23.9, 23.7, 13.9. HRMS (ESI) for $C_{14}H_{26}O_3Na$ [M+H]$^+$ calculated: 265.1780, found: 265.1788.

4.2.6. Ethyl 2-acetyl-2-pentylheptanoate 6

R_f = 0.4 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.13 (q, J = 7.2 Hz, 2H), 2.05 (s, 3H), 1.83–1.65 (m, 4H), 1.23–1.16 (m, 11H), 1.03–1.00 (m, 4H), 0.84–0.78 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.6, 172.9, 63.6, 61.1, 32.3, 31.2, 26.7, 23.6, 22.5, 14.2, 14.1. HRMS (ESI) for $C_{16}H_{30}O_3Na$ [M+H]$^+$ calculated: 293.2093, found: 293.2099.

4.2.7. Ethyl 2-acetyl-2-hexyloctanoate 7

R_f = 0.4 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.16 (q, J = 7.2 Hz, 2H), 2.09 (s, 3H), 1.86–1.75 (m, 4H), 1.30–1.19 (m, 15H), 1.08–1.03 (m, 4H), 0.92–0.82 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 205.7, 172.9, 64.0, 61.2, 31.9, 31.8, 31.7, 31.3, 29.8, 29.6, 27.6, 26.8, 23.9, 22.7, 14.3, 14.2. HRMS (ESI) for $C_{18}H_{34}O_3Na$ [M+H]$^+$ calculated: 321.2406, found: 321.2413.

4.2.8. Ethyl 2-acetyl-2-allylpent-4-enoate 8

R_f = 0.5 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.67–5.46 (m, 2H), 5.10–5.02 (m, 4H), 4.16 (q, J = 7.2 Hz, 2H), 2.60–2.55 (m, 4H), 2.09 (s, 3H), 1.23 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 204.2, 171.6, 132.3, 119.3, 63.4, 61.5, 36.1, 27.1, 14.2. HRMS (ESI) for $C_{12}H_{18}O_3Na$ [M+H]$^+$ calculated: 233.1154, found: 233.1158.

4.2.9. Ethyl 2-acetyl-2-(but-3-enyl)hex-5-enoate 9

R_f = 0.7 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.85–5.66 (m, 2H), 5.04–4.19 (m, 4H), 4.18 (q, J = 7 Hz, 2H), 2.10 (s, 3H), 2.06–1.70 (m, 8H), 1.27–1.20 (m, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.1, 172.4, 137.7, 115.3, 63.1, 61.4, 30.6, 28.3, 26.9, 14.2. HRMS (ESI) for $C_{14}H_{22}O_3Na$ [M+H]$^+$ calculated: 261.1467, found: 261.1469.

4.2.10. Ethyl 2,2-dibenzyl-3-oxobutanoate 10

R_f = 0.6 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.31–7.14 (m, 10H), 4.15 (q, J = 7.2 Hz, 2H), 3.26 (s, 4H), 2.00 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.8, 171.9, 136.5, 130.2, 128.5, 127.1, 66.3, 61.5, 40.0, 29.2, 14.0. HRMS (ESI) for $C_{20}H_{22}O_3Na$ [M+H]$^+$ calculated: 333.1467, found: 333.1461.

4.2.11. Ethyl 2,2-bis(4-methoxybenzyl)-3-oxobutanoate 11

R_f = 0.6 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.11–6.77 (m, 8H), 2.12 (q, J = 7.2 Hz, 2H), 3.77 (s, 6H), 3.14 (s, 4H), 1.95 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 206.5, 172.1, 158.6, 131.2, 128.4, 113.8, 66.5, 66.4, 61.4, 55.3, 39.1, 29.4, 14.1. HRMS (ESI) for $C_{22}H_{26}O_5Na$ [M+H]$^+$ calculated: 393.1678, found: 393.1671.

4.2.12. Ethyl 2-acetyl-2-(prop-2-ynyl)pent-4-ynoate 12

R_f = 0.5 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.21 (q, J = 7.2 Hz, 2H), 3.02–2.82 (m, 4H), 2.19 (s, 3H), 2.02–1.99 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 201.0, 169.3, 78.7, 72.1, 62.4, 26.2, 21.9, 14.1. HRMS (ESI) for $C_{12}H_{14}O_3Na$ [M+H]$^+$ calculated: 229.0841, found: 229.0847.

4.2.13. Ethyl 1-acetylcyclopent-3-enecarboxylate 13

Compound **8** (300 mg, 1.43 mmol) was dissolved in anhydrous degassed CH_2Cl_2 (250 mL), after which Grubbs first generation catalyst (Grubbs-I; 0.071 mol, 58.8 mg) was added. The solution was then stirred at room temperature under an argon atmosphere

for 12 h, after which air was bubbled into the reaction mixture to quench the catalyst, and the solvent was evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:30) to give ring closing metathesis product **13** (230 mg, 88%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.59–5.53 (m, 2H), 4.19 (q, J = 7.2 Hz, 2H), 2.90 (s, 4H), 2.15 (s, 3H), 1.23 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 202.8, 173.0, 127.8, 65.5, 61.7, 39.3, 26.0, 22.9, 22.7, 14.1. HRMS (ESI) for $C_{10}H_{14}O_3Na$ $[M+H]^+$ calculated: 205.0841, found: 205.0845.

4.2.14. Ethyl 1-acetylcyclopentanecarboxylate 14

To a solution of olefin **13** (240 mg, 1.32 mmol) in anhydrous methanol (6 mL) was added a catalytic amount of Pd/C (25 mg) under an argon atmosphere. The mixture was then put into a Parr apparatus under a hydrogen atmosphere for 5 h. The completion of the reaction was determined by TLC analysis. The solid catalyst was filtered off and the solvent was removed under reduced pressure. The crude residue was directly loaded in the column and purified via flash column chromatography. R_f = 0.6 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.15 (q, J = 7.2 Hz, 2H), 2.21–2.03 (m, 7H), 1.64–1.57 (m, 4H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 204.2, 173.7, 67.1, 61.5, 33.2, 26.6, 25.8, 14.2. HRMS (ESI) for $C_{10}H_{16}O_3Na$ $[M+H]^+$ calculated: 207.0997, found: 207.0992.

4.2.15. (*Z*)-Ethyl 1-acetylcyclohept-4-enecarboxylate 15

Prepared in 84% yield as a colourless oil analogous to the route described for **13** from the ring closing metathesis precursor compound **9** (320 mg, 1.34 mmol). R_f = 0.6 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.67–5.62 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 2.21–2.03 (m, 11H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.0, 173.0, 130.9, 64.1, 61.5, 31.0, 26.2, 24.6, 14.2. HRMS (ESI) for $C_{12}H_{18}O_3Na$ $[M+H]^+$ calculated: 233.1154, found: 233.1161.

4.2.16. Ethyl 1-acetylcycloheptanecarboxylate 16

Prepared in 88% yield as a colourless oil analogous from olefin **15** (230 mg, 1.095 mmol) as described above for the synthesis of compound **14**. R_f = 0.6 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.17 (q, J = 7.2 Hz, 2H), 2.20–1.93 (m, 7H), 1.60–1.51 (m, 8H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.3, 173.7, 63.8, 61.3, 32.5, 30.1, 26.1, 23.9, 14.1. HRMS (ESI) for $C_{12}H_{20}O_3Na$ $[M+H]^+$ calculated: 235.1310, found: 235.1318.

4.3. Synthesis of enantiopure 'alcohols 17–32' by whole cell mediate bioreduction (general procedure)

The dried cells obtained from the culture collection were moistened with a rehydration fluid (peptone 10 g, yeast extract 2 g, $MgSO_4{\cdot}7H_2O$ 1 g, distilled water 1 L, pH 7.0). It was then streaked into several Petri dishes (containing the same components with agar 15.0 g/L is added) and then incubated at 25 °C in an incubator for 24 h. For the biotransformation with NBRC 3319, a liquid medium (glucose 40.0 g, meat extract 5.0 g, NaCl 5.0 g, peptone 10.0 g, $CaCO_3$ 40.0 g in 1 L of distilled water) was prepared without agar, and then the grown cells of *K. pneumoniae* were transferred to this medium through an inoculating loop. The content was incubated in an incubator shaker for 48 h, after which the parent di-substituted β-ketoesters **1**–**16** were directly added to the growing culture medium. The reaction was monitored occasionally by TLC analysis. After completion of the reaction, the product was isolated by extraction with EtOAc several times. It was then purified through silica gel chromatography to afford the product alcohols **17**–**32**.

4.3.1. (*S*)-Ethyl 3-hydroxy-2,2-dimethylbutanoate 17

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +9.8 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.11 (q, J = 7.2 Hz, 2H), 3.82 (q, J = 6.6 Hz, 1H), 2.65 (br, 1H, OH), 1.22 (t, J = 7.2 Hz, 3H), 1.12–1.08 (m, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 178.0, 72.5, 60.8, 47.1, 25.8, 22.3, 19.9, 17.8, 14.2. HRMS (ESI) for $C_8H_{16}O_3Na$ $[M+H]^+$ calculated: 183.0997, found: 183.0989.

4.3.2. (*S*)-Ethyl 2,2-diethyl-3-hydroxybutanoate 18

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +11.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.18 (q, J = 7.2 Hz, 2H), 3.91 (q, J = 6.4 Hz, 1H), 2.88 (s, 1H), 1.86–1.65 (m, 3H), 1.55–1.44 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.13 (d, J = 6.6 Hz, 3H), 0.90–0.85 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 177.3, 70.0, 60.7, 53.9, 25.8, 23.9, 18.1, 14.5, 8.9. HRMS (ESI) for $C_{10}H_{20}O_3Na$ $[M+H]^+$ calculated: 211.1310, found: 211.1319.

4.3.3. (*S*)-Ethyl 2-(1-hydroxyethyl)-2-propylpentanoate 19

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +4.5 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.14 (q, J = 7 Hz, 2H), 3.88 (q, J = 6.4 Hz, 1H), 2.93 (br, 1H, OH), 1.71–1.50 (m, 5H), 1.46–0.99 (m, 9H), 0.93–0.81 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 177.3, 70.3, 60.6, 53.5, 36.1, 34.2, 17.9, 17.7, 15.1, 14.8, 14.3. HRMS (ESI) for $C_{12}H_{24}O_3Na$ $[M+H]^+$ calculated: 239.1623, found: 239.1628.

4.3.4. (*S*)-Ethyl 2-butyl-2-(1-hydroxyethyl)hexanoate 20

R_f = 0.3 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +12.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.18 (q, J = 7.2 Hz, 2H), 3.93 (q, J = 6.4 Hz, 1H), 2.90 (s, 1H), 1.79–1.64 (m, 3H), 1.62–1.12 (m, 14H), 0.92–0.85 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 177.4, 70.3, 60.6, 53.4, 33.5, 31.6, 26.6, 23.6, 23.4, 17.9, 14.4, 14.1, 14.0. HRMS (ESI) for $C_{14}H_{28}O_3Na$ $[M+H]^+$ calculated: 267.1936, found: 267.1939.

4.3.5. (*S*)-Ethyl 2-(1-hydroxyethyl)-2-isobutyl-4-methylpentanoate 21

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +10.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.19–4.08 (m, 3H), 3.67–3.60 (m, 1H), 2.04–1.91 (m, 1H), 1.71–1.59 (m, 3H), 1.49–1.42 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.13 (d, J = 6.6 Hz, 3H), 0.88–0.81 (m, 12H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 178.9, 69.6, 60.7, 52.3, 45.4, 42.8, 25.2, 24.6, 24.5, 23.9, 23.5, 16.9, 14.1. HRMS (ESI) for $C_{14}H_{28}O_3Na$ $[M+H]^+$ calculated: 267.1936, found: 267.1939.

4.3.6. (*S*)-Ethyl 2-(1-hydroxyethyl)-2-pentylheptanoate 22

R_f = 0.3 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +16.4 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.15 (q, J = 7.2 Hz, 2H), 3.90 (q, J = 6.4 Hz, 1H), 2.89–2.86 (m, 1H), 1.73–1.58 (m, 3H), 1.33–1.21 (m, 14H), 1.12–1.09 (m, 5H), 0.87–0.81 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 177.5, 70.3, 60.6, 53.5, 33.8, 32.9, 32.6, 31.9, 24.1, 22.6, 18.0, 14.4, 14.2. HRMS (ESI) for $C_{16}H_{32}O_3Na$ $[M+H]^+$ calculated: 295.2249, found: 295.2241.

4.3.7. (*S*)-Ethyl 2-hexyl-2-(1-hydroxyethyl)octanoate 23

R_f = 0.3 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +15.8 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.16 (q, J = 7.2 Hz, 2H), 3.92–3.85 (m, 1H), 2.67 (s, 1H), 1.64–1.59 (m, 3H), 1.29–1.22 (m, 16H), 1.13–1.10 (m, 7H), 0.85 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 177.5, 70.3, 60.7, 53.6, 33.8, 31.9, 31.8, 31.8, 30.3, 30.1, 24.4, 22.8, 18.0, 14.4, 14.2. HRMS (ESI) for $C_{18}H_{36}O_3Na$ $[M+H]^+$ calculated: 323.2562, found: 323.2567.

4.3.8. (*S*)-Ethyl 2-allyl-2-(1-hydroxyethyl)pent-4-enoate 24

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +23.3 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.94–5.62 (m, 2H), 5.11–5.03 (m, 4H), 4.16 (q, J = 7.2 Hz, 2H), 3.89 (q, J = 6.4 Hz, 1H), 2.55–2.05 (m, 4H),

1.29–1.15 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 175.7, 134.3, 133.9, 118.5, 118.2, 70.7, 60.9, 54.0, 37.7, 36.4, 18.2, 14.4. HRMS (ESI) for $C_{12}H_{20}O_3Na$ $[M+H]^+$ calculated: 235.1310, found: 235.1318.

4.3.9. (*S*)-Ethyl 2-(but-3-enyl)-2-(1-hydroxyethyl)hex-5-enoate 25

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +19.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.85–5.68 (m, 2H), 5.05–4.91 (m, 4H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.00–3.93 (m, 1H), 3.06 (d, *J* = 6.4 Hz, 1H), 2.14–1.48 (m, 8H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 176.8, 138.7, 138.3, 114.9, 114.7, 70.2, 60.9, 53.2, 33.1, 31.3, 29.0, 28.8, 17.9, 14.4. HRMS (ESI) for $C_{14}H_{24}O_3Na$ $[M+H]^+$ calculated: 263.1623, found: 263.1629.

4.3.10. (*S*)-Ethyl 2,2-dibenzyl-3-hydroxybutanoate 26

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +33.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.26–7.15 (m, 10H), 4.11–3.98 (m, 3H), 3.32–2.86 (m, 4H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 176.4, 137.9, 137.6, 130.7, 130.2, 128.4, 128.2, 126.8, 126.7, 69.2, 61.0, 55.8, 39.7, 38.6, 18.1, 14.0. HRMS (ESI) for $C_{20}H_{24}O_3Na$ $[M+H]^+$ calculated: 335.1623, found: 335.1627.

4.3.11. (*S*)-Ethyl 3-hydroxy-2,2-bis(4-methoxybenzyl)butanoate 27

R_f = 0.3 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +28.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.15–7.06 (m, 4H), 6.84–6.78 (m, 4H), 4.17–3.95 (m, 3H), 3.81–3.13 (m, 6H), 3.21–2.73 (m, 4H), 1.31–1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 176.4, 158.4, 131.6, 131.2, 129.8, 129.4, 113.8, 113.6, 69.3, 60.9, 55.9, 55.4, 38.8, 37.7, 18.2, 14.1. HRMS (ESI) for $C_{22}H_{28}O_5Na$ $[M+H]^+$ calculated: 395.1834, found: 395.1839.

4.3.12. (*S*)-Ethyl 2-(1-hydroxyethyl)-2-(prop-2-ynyl)pent-4-ynoate 28

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +15.6 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.21 (q, *J* = 7 Hz, 2H), 4.03 (q, *J* = 6.2 Hz, 1H), 2.92–2.55 (m, 5H), 2.02–2.02 (m, 2H), 1.30–1.18 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 173.2, 80.3, 79.8, 71.6, 71.5, 70.5, 61.6, 53.2, 22.4, 22.1, 19.0, 14.3. HRMS (ESI) for $C_{12}H_{16}O_3Na$ $[M+H]^+$ calculated: 231.0997, found: 231.0992.

4.3.13. (*S*)-Ethyl 1-(1-hydroxyethyl)cyclopent-3-enecarboxylate 29

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +38.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.64–5.52 (m, 2H), 4.17 (q, *J* = 7 Hz, 2H), 3.92 (q, *J* = 6.4 Hz, 1H), 2.86–2.66 (m, 4H), 2.56–2.40 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 177.5, 129.3, 128.2, 71.6, 61.1, 57.1, 40.5, 38.5, 18.2, 14.3. HRMS (ESI) for $C_{10}H_{16}O_3Na$ $[M+H]^+$ calculated: 207.0997, found: 207.0991.

4.3.14. (*S*)-Ethyl 1-(1-hydroxyethyl)cyclopentanecarboxylate 30

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +32.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.16 (q, *J* = 7.2 Hz, 2H), 3.73–3.70 (m, 1H), 2.89–2.87 (m, 1H), 2.16–2.07 (m, 1H), 2.05–1.94 (m, 1H), 1.87–1.80 (m, 1H), 1.71–1.57 (m, 4H), 1.49–1.42 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 177.7, 72.8, 60.9, 59.1, 34.4, 33.0, 26.2, 25.8, 19.7, 14.4. HRMS (ESI) for $C_{10}H_{18}O_3Na$ $[M+H]^+$ calculated: 209.1154, found: 209.1158.

4.3.15. (*S,Z*)-Ethyl 1-(1-hydroxyethyl)cyclohept-4-enecarboxylate 31

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +22.7 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.72–5.64 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.79–3.73 (m, 1H), 2.63–2.59 (m, 1H), 2.63–1.81 (m, 8H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 176.7, 131.1, 131.0, 72.1, 60.8, 54.8, 31.5, 31.3, 24.8, 24.5, 19.1, 14.5. HRMS (ESI) for $C_{12}H_{20}O_3Na$ $[M+H]^+$ calculated: 235.1310, found: 235.1318.

4.3.16. (*S*)-Ethyl 1-(1-hydroxyethyl)cycloheptanecarboxylate 32

R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +29.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.17 (q, *J* = 7.2 Hz, 2H), 3.74–3.64 (m, 1H), 2.58–2.54 (m, 1H), 2.17–2.06 (m, 1H), 1.92–1.88 (m, 2H), 1.53–1.42 (m, 9H), 1.27 (t, *J* = 7 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 177.4, 73.0, 60.7, 54.7, 32.7, 32.5, 30.4, 30.1, 24.3, 23.7, 18.9, 14.3. HRMS (ESI) for $C_{12}H_{22}O_3Na$ $[M+H]^+$ calculated: 237.2910, found: 237.2917.

4.3.17. (*S*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)-2,2-diethylbutanoate 33

To a solution of alcohol **18** (600 mg, 3.2 mmol) in 10 mL of CH_2Cl_2, under argon at 0 °C, were successively added dry 2,6-lutidine (0.63 mL, 5.44 mmol) and *t*-$BuMe_2SiOTf$ (1.1 mL, 4.8 mmol). The reaction mixture was stirred at 0 °C to room temperature for 4 h and then quenched by adding water. The aqueous phase was reextracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexane, 1:40) of the oily residue afforded 900 mg (93%) of the silyloxy derivative **33** as a light yellow oil. R_f = 0.4 (EtOAc/hexane, 1:40). $[\alpha]_D^{28}$ = +30.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.19–3.97 (m, 3H), 1.75–1.58 (m, 4H), 1.27–1.17 (m, 6H), 0.99–0.80 (m, 15H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 175.6, 72.5, 60.0, 54.9, 25.9, 24.4, 24.3, 19.4, 18.1, 14.4, 9.5, 9.1, −3.8, −5.0. HRMS (ESI) for $C_{16}H_{34}O_3SiNa$ $[M+H]^+$ calculated: 325.2175, found: 325.2179.

4.3.18. (*S*)-Ethyl 2-allyl-2-(1-(*tert*-butyldimethylsilyloxy)ethyl) pent-4-enoate 34

Prepared in 87% yield as light yellow oil analogous to the route described for **33** from the enantiopure alcohol **24**. R_f = 0.4 (EtOAc/hexane, 1:40). $[\alpha]_D^{28}$ = +18.9 (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.96–5.67 (m, 2H), 5.07–4.98 (m, 4H), 4.14–4.01 (m, 3H), 2.41–2.38 (m, 4H), 1.28–1.10 (m, 6H), 0.86 (s, 9H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 174.7, 135.2, 117.5, 72.6, 60.5, 54.9, 37.2, 36.6, 26.0, 19.5, 18.2, 14.5, −3.7, −4.8. HRMS (ESI) for $C_{18}H_{34}O_3SiNa$ $[M+H]^+$ calculated: 349.2175, found: 349.2171.

4.3.19. (*S*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)-2,2-bis(4-methoxybenzyl)butanoate 35

Prepared in 80% yield as light yellow oil analogous to the route described for **33** from the enantiopure alcohol **27**. R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +44.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.26–7.01 (m, 4H), 6.78–6.73 (m, 4H), 4.23–4.03 (m, 3H), 3.77 (s, 6H), 3.04–2.84 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.03–0.91 (m, 12H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 174.8, 158.2, 158.1, 132.1, 131.4, 130.9, 130.2, 113.4, 113.2, 72.3, 60.3, 57.2, 55.2, 40.2, 36.8, 26.1, 20.0, 18.3, 14.1, −3.3, −4.8. HRMS (ESI) for $C_{28}H_{42}O_5SiNa$ $[M+H]^+$ calculated: 509.2699, found: 509.2692.

4.3.20. (*S*)-Ethyl 1-(1-(*tert*-butyldimethylsilyloxy)ethyl)cyclopent-3-enecarboxylate 36

Prepared in 86% yield as light yellow oil analogous to the route described for **33** from the enantiopure alcohol **29**. R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +23.4 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.63–5.50 (m, 2H), 4.21–4.08 (m, 3H), 2.87–2.35 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 0.83

(s, 9H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 176.7, 129.4, 128.3, 72.1, 60.7, 58.8, 38.4, 38.2, 26.1, 25.9, 19.2, 18.1, 14.3, −3.7, −4.9. HRMS (ESI) for $C_{16}H_{30}O_3SiNa$ $[M+H]^+$ calculated: 321.1862, found: 321.1867.

4.3.21. (*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,3-diethylpentan-2-one 37

To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (484 mg, 4.967 mmol) in dry benzene (9 mL) at 0 °C under nitrogen was added dropwise trimethylaluminum (2.0 M in toluene, 1 mL, 4.967 mmol). The reaction mixture was stirred for 1 h and then treated with a solution of (*S*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-2,2-diethylbutanoate **33** (600 mg, 1.987 mmol) in dry benzene (3 mL). The mixture was stirred at room temperature overnight and poured into a saturated aqueous ammonium chloride (20 mL). The resulting precipitate was filtered through a pad of Celite, after which the filtrate was extracted with dichloromethane (3 × 75 mL) and the combined extracts washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated. The crude Weinreb amide was dissolved in dry diethyl ether, and then a freshly prepared MeMgI solution (3 mmol in Et_2O) was added at 0 °C. The reaction mixture was then allowed to reach room temperature. After 6 h, the reaction was quenched by the addition of saturated NH_4Cl solution, and then the mixture was extracted with diethyl ether. The combined organic extract was then dried over anhydrous $NaSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane, 1:30) to give compound **37** in 80% yield as a colourless liquid. R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +11.4 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.87 (q, *J* = 6.4 Hz, 1H), 2.15 (s, 3H), 1.89–1.58 (m, 3H), 1.52–1.38 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.82–0.71 (m, 6H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 213.4, 71.4, 59.4, 28.9, 26.0, 23.4, 22.5, 19.4, 18.2, 8.7, 8.6, −3.9, −4.9. HRMS (ESI) for $C_{15}H_{32}O_2SiNa$ $[M+H]^+$ calculated: 295.2069, found: 295.2075.

4.3.22. (*S*)-3-Allyl-3-(1-(*tert*-butyldimethylsilyloxy)ethyl)hex-5-en-2-one 38

Prepared in 80% yield as colourless oil analogous to the route described for **37** from the TBS protected ester compound **34**. R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +5.8 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.81–5.62 (m, 2H), 5.13–5.03 (m, 4H), 3.90 (q, *J* = 6.4 Hz, 1H), 2.40–2.25 (m, 4H), 2.19 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 211.9, 134.4, 134.2, 118.2, 71.8, 59.4, 36.3, 35.4, 29.1, 26.1, 19.3, 18.2, −3.8, −4.8. HRMS (ESI) for $C_{17}H_{32}O_2SiNa$ $[M+H]^+$ calculated: 319.2069, found: 319.2062.

4.3.23. (*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,3-bis(4-methoxybenzyl)pentan-2-one 39

Prepared in 79% yield as colourless oil analogous to the route described for **37** from the TBS protected ester compound **35**. R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +22.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.05–7.00 (m, 2H), 6.91–6.73 (m, 6H), 4.00–3.78 (m, 7H), 3.41 (d, *J* = 15.8 Hz, 1H), 2.91 (s, 2H), 2.74 (d, *J* = 15.8 Hz, 1H), 2.30 (s, 3H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 212.4, 157.3, 130.7, 129.9, 129.5, 129.2, 113.1, 112.7, 70.6, 59.6, 54.5, 35.8, 34.6, 29.1, 25.3, 18.8, 17.4, −4.6, −5.7. HRMS (ESI) for $C_{27}H_{40}O_4SiNa$ $[M+H]^+$ calculated: 479.2594, found: 479.2598.

4.3.24. (*S*)-1-(1-(1-(*tert*-Butyldimethylsilyloxy)ethyl)cyclopent-3-enyl)ethanone 40

Prepared in 82% yield as a colourless oil analogous to the route described for **37** from the TBS protected ester compound **36**. R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +39.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.62–5.51 (m, 2H), 4.06 (q, *J* = 6.2 Hz, 1H), 2.78–2.37 (m, 2H), 2.19 (s, 3H), 1.32–1.23 (m, 2H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 211.5, 129.9, 128.0, 72.3, 64.7, 38.2, 37.2, 27.9, 26.0, 19.6, 18.2, −3.7, −4.8. HRMS (ESI) for $C_{15}H_{28}O_2SiNa$ $[M+H]^+$ calculated: 291.1756, found: 291.1759.

4.4. TBS deprotection of compounds 41–44 (general procedure)

A solution of TBS protected methyl ketone compounds were taken in dry MeOH. Next, pyridinium *p*-toluenesulfonate (1 equiv) was added to the reaction mixture at room temperature for 6 h. After completion of the reaction as indicated by TLC analysis, MeOH was evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:5) to afford as a viscous liquid.

4.4.1. (*S*)-3,3-Diethyl-4-hydroxypentan-2-one 41

R_f = 0.2 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +37.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.87 (q, *J* = 6.4 Hz, 1H), 2.15 (s, 3H), 1.89–1.58 (m, 4H), 1.52–1.38 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.82–0.71 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 213.4, 71.4, 59.4, 28.9, 23.4, 22.5, 19.4, 8.7, 8.6. HRMS (ESI) for $C_9H_{18}O_2Na$ $[M+H]^+$ calculated: 181.1204, found: 181.1208.

4.4.2. (*S*)-3-Allyl-3-(1-hydroxyethyl)hex-5-en-2-one 42

R_f = 0.2 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +28.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.81–5.62 (m, 2H), 5.13–5.03 (m, 4H), 3.90 (q, *J* = 6.4 Hz, 1H), 2.72–2.61 (m, 1H), 2.40–2.25 (m, 4H), 2.19 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 211.9, 134.4, 134.2, 118.2, 71.8, 59.3, 36.3, 35.4, 29.1, 19.3. HRMS (ESI) for $C_{11}H_{18}O_2Na$ $[M+H]^+$ calculated: 205.1204, found: 205.1208.

4.4.3. (*S*)-4-Hydroxy-3,3-bis(4-methoxybenzyl)pentan-2-one 43

R_f = 0.2 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +44.5 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.05–6.73 (m, 8H), 4.00–3.79 (m, 1H), 3.78 (s, 6H), 3.41 (d, *J* = 15.8 Hz, 1H), 2.91 (s, 2H), 2.74 (d, *J* = 5.8 Hz, 1H), 2.30 (s, 3H), 1.10 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 212.3, 157.3, 130.7, 129.9, 129.4, 129.2, 113.0, 112.7, 70.5, 59.6, 54.5, 35.8, 34.6, 29.1, 18.8. HRMS (ESI) for $C_{21}H_{26}O_4Na$ $[M+H]^+$ calculated: 365.1729, found: 365.1736.

4.4.4. (*S*)-1-(1-(1-Hydroxyethyl)cyclopent-3-enyl)ethanone 44

R_f = 0.2 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +29.2 (*c* 0.7, $CHCl_3$).^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.62–5.51 (m, 2H), 4.06 (q, *J* = 6.2 Hz, 1H), 2.86–2.84 (m, 1H), 2.78–2.37 (m, 2H), 2.19 (s, 3H), 1.32–1.23 (m, 2H), 1.04 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 211.5, 129.9, 128.0, 72.3, 64.7, 38.2, 37.2, 27.9, 19.6. HRMS (ESI) for $C_9H_{14}O_2Na$ $[M+H]^+$ calculated: 177.0891, found: 177.0896.

4.5. Ethyl 2-acetyl-2-methylpent-4-enoate 45

At first, KO^{t}Bu (1.76 g, 15.7 mmol) and ^{t}BuOH (0.13 mL, 1.413 mmol) were added to a solution of ethylacetoacetate (2 mL, 15.7 mmol) in dry THF at 0 °C under a nitrogen atmosphere. The reaction mixture was then stirred at 0 °C for 30 min, and then freshly distilled allyl bromide (1.3 mL, 15.7 mmol) was added dropwise. The reaction mixture was then stirred at reflux. After 12 h, the mixture was cooled to room temperature, and then ice-cooled water was added to quench the reaction. The THF was evaporated under vacuum, and diethyl ether was added. The product was extracted with diethyl ether, and the combined organic extracts were dried over $MgSO_4$, and concentrated. The crude organic compound was dissolved in dry THF and then NaH (60%) (471 mg, 11.764 mmol) was added to the mixture portion wise at 0 °C under a nitrogen atmosphere. The mixture was stirred

at 0 °C for 30 min and then CH_3I (0.88 mL, 14.117 mmol) was added dropwise. The reaction mixture was stirred at reflux. After 12 h, the mixture was cooled to room temperature, and then ice-cooled water was added to quench the reaction. The THF was evaporated under vacuum, and diethyl ether was added. The product was extracted with diethyl ether, and the combined organic extracts were dried over $MgSO_4$, and concentrated residue was purified by flash chromatography (EtOAc/hexane, 1:30) to give pure compound **45** (1.8 g, 82%) as a colourless liquid. R_f = 0.3 (EtOAc/hexane, 1:30). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.74–5.53 (m, 1H), 5.11–5.04 (m, 2H), 5.18 (q, J = 7.2 Hz, 2H), 2.68–2.41 (m, 2H), 2.13 (s, 3H), 1.13–1.05 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 205.1, 172.6, 132.8, 119.1, 61.4, 59.5, 39.5, 26.3, 19.0, 14.2. HRMS (ESI) for $C_{10}H_{16}O_3Na$ $[M+H]^+$ calculated: 207.0997, found: 207.0991.

4.5.1. Bioreduction of compound 45

Bioreduction of compound **45** with *K. pneumoniae* (NBRC 3319) was carried out as described above for the synthesis of compounds **17**–**32**, to give an inseparable mixture of compounds **47**/**49** (70%) as a colourless liquid.

4.6. (*R*)-Ethyl 2-((*S*)-1-hydroxyethyl)-2-methylpent-4-enoate 47/49

R_f = 0.3 (EtOAc/hexane, 1:10). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.88–5.59 (m, 1H), 5.10–5.02 (m, 2H), 4.22–4.12 (m, 2H), 3.93–3.83 (m, 1H), 2.74 (d, J = 7.2 Hz, 1H), 2.57–2.18 (m, 2H), 1.30–1.11 (m, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 176.8, 176.3, 134.3, 133.5, 118.4, 118.1, 72.0, 71.4, 60.8, 60.7, 51.1, 50.9, 41.1, 40.0, 18.4, 17.8, 17.1, 14.4. HRMS (ESI) for $C_{10}H_{18}O_3Na$ $[M+H]^+$ calculated: 209.1154, found: 209.1158.

4.7. Ethyl 2-((*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl)-2-methylpent-4-enoate (TBS protected)

Prepared in 85% yield as a colourless oil analogous to the route described for **33** from the enantiopure secondary alcohol **47**/**49** as inseparable mixture. R_f = 0.6 (EtOAc/hexane, 1:20). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.82–5.59 (m, 1H), 5.05–4.98 (m, 2H), 4.21–3.95 (m, 3H), 2.47–1.97 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.09–0.84 (m, 15H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 175.8, 175.6, 134.8, 134.4, 117.8, 117.7, 73.0, 72.8, 60.4, 52.4, 52.3, 41.7, 40.5, 26.0, 25.9, 19.5, 18.3, 18.2, 18.1, 15.5, 14.8, 14.4, 14.4, −3.8, −3.8, −4.8, −5.1. HRMS (ESI) for $C_{16}H_{32}O_3SiNa$ $[M+H]^+$ calculated: 323.2018, found: 323.2012.

4.8. 2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2-methylpent-4-en-1-ol 51/53

At first, TBS protected enantiopure secondary alcohol compounds **47**/**49** (550 mg, 1.83 mmol) was dissolved in dry DCM (8 mL), and the solution was cooled to −30 °C. A solution of DIBAL-H (1 M in cyclohexane; 4.5 mL, 4.5 mmol) was then added over 15 min. The reaction mixture was stirred for 4 h at the same temperature, after which the reaction mixture was quenched with a saturated solution of sodium potassium tartrate and stirred for a further 1.5 h. The mixture was filtered through a pad of Celite to remove the solid residues and extracted several times with DCM. The combined DCM extracts were then evaporated under vacuum and the residue was purified by flash chromatography (EtOAc/hexane, 1:10) to give compounds **51**/**53** (190 mg faster moving compound and 210 mg slower moving compound) as a colourless liquid. The faster moving compound was later assigned as compound **51** and its absolute configuration was confirmed as reported earlier.[7c]

4.8.1. (*S*)-2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2-methylpent-4-en-1-ol 51

R_f = 0.4 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +6.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.96–5.75 (m, 1H),5.13–5.05 (m, 2H), 3.80–3.71 (m, 2H), 3.35–3.20 (m, 2H), 2.46–2.36 (m, 1H), 2.14–2.03 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.66 (s, 3H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 135.0, 117.9, 76.0, 67.3, 41.7, 39.6, 26.0, 18.4, 18.1, −3.9, −4.9. HRMS (ESI) for $C_{14}H_{30}O_2SiNa$ $[M+H]^+$ calculated: 281.2913, found: 281.2918.

4.8.2. (*R*)-2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2-methylpent-4-en-1-ol 53

R_f = 0.4 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +11.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.69–5.69 (m, 1H), 5.07–4.99 (m, 2H), 3.75–3.69 (m, 2H), 3.34–3.13 (m, 2H), 2.05–1.79 (m, 2H), 1.18 (d, J = 6.4 Hz, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 134.5, 117.7, 76.0, 68.7, 41.7, 39.0, 26.0, 19.7, 18.3, 18.1, −4.0, −4.9. HRMS (ESI) for $C_{14}H_{30}O_2SiNa$ $[M+H]^+$ calculated: 281.2913, found: 281.2918.

4.9. 3-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methylhex-5-en-2-one 55/57

To a solution of **51**/**53** (faster moving compound) (160 mg, 0.62 mmol) in dry CH_2Cl_2 (4 mL) were added TEMPO (19 mg, 0.124 mmol) and BAIB (399 mg, 1.24 mmol). After stirring at room temperature for 6 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and then washed with satd aq $Na_2S_2O_3$ (4 mL). The organic layer was then dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give a crude aldehyde, which was dissolved in dry diethyl ether, after which a freshly prepared MeMgI solution (3 mmol in Et_2O) was added at 0 °C. The reaction mixture was then allowed to reach room temperature. After 6 h, the reaction was quenched by the addition of saturated NH_4Cl solution, and then the mixture was extracted with diethyl ether. The combined organic extract was dried over anhydrous $NaSO_4$, and evaporated in vacuo. The crude product was further oxidized by BAIB/TEMPO according to the procedure described above. The crude methyl ketone compound was purified by flash chromatography (EtOAc/hexane, 1:30) to give the pure methyl ketone compounds **55**/**57** in 87% yield.

4.9.1. (*R*)-3-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methylhex-5-en-2-one 55

R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +28.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.71–5.50 (m, 1H), 5.06–4.99 (m, 2H), 3.96 (q, J = 6.4 Hz, 1H), 2.54–2.44 (m, 1H), 2.13 (s, 3H), 2.04–1.93 (m, 1H), 1.05 (d, J = 6.2 Hz, 6H), 0.86 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 213.0, 134.0, 118.1, 73.8, 56.6, 40.6, 28.7, 26.0, 18.7, 18.1, 16.1, −3.8, −4.9. HRMS (ESI) for $C_{15}H_{30}O_2SiNa$ $[M+H]^+$ calculated: 293.1913, found: 293.1921.

4.9.2. (*S*)-3-((*S*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methylhex-5-en-2-one 57

R_f = 0.57 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +8.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.74–5.52 (m, 1H), 5.09–4.95 (m, 2H), 3.92 (q, J = 6.4 Hz, 1H), 2.54–2.40 (m, 1H), 2.15 (s, 3H), 2.02–1.94 (m, 1H), 1.06 (d, J = 6.2 Hz, 6H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 213.2, 134.3, 118.2, 73.3, 56.5, 40.7, 28.2, 26.2, 18.5, 18.2, 16.0, −3.7, −4.8. HRMS (ESI) for $C_{15}H_{30}O_2SiNa$ $[M+H]^+$ calculated: 293.1913, found: 293.1919.

4.10. 3-((*S*)-1-Hydroxyethyl)-3-methylhex-5-en-2-one 59/61

The deprotection of the TBS group was carried out as described above for the general procedure for the TBS deprotection of compounds **41**–**44**.

4.10.1. (*R*)-3-((*S*)-1-Hydroxyethyl)-3-methylhex-5-en-2-one 59

R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +24.6 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.73–5.53 (m, 1H), 5.11–5.03 (m, 2H), 3.97 (q, *J* = 6.4 Hz, 1H), 2.42–2.27 (m, 2H), 2.16 (s, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 215.4, 133.1, 118.7, 71.2, 55.7, 41.0, 27.6, 17.8, 16.5. HRMS (ESI) for $C_9H_{16}O_2Na$ $[M+H]^+$ calculated: 179.1048, found: 179.1041.

4.10.2. (*S*)-3-((*S*)-1-Hydroxyethyl)-3-methylhex-5-en-2-one 61

R_f = 0.28 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +16.7 (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.73–5.58 (m, 1H), 5.14–5.05 (m, 2H), 3.94 (q, *J* = 6.4 Hz, 1H), 2.40–2.29 (m, 2H), 2.15 (s, 3H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 215.2, 133.0, 118.5, 71.4, 55.6, 41.1, 27.8, 17.5, 16.2. HRMS (ESI) for $C_9H_{16}O_2Na$ $[M+H]^+$ calculated: 179.1048, found: 179.1041.

4.11. Ethyl 2-acetyl-2-benzylpent-4-enoate 46

Prepared in 70% yield as colourless oil analogous to the route described above for the synthesis of **45**. R_f = 0.3 (EtOAc/hexane, 1:30). ^1H NMR ($CDCl_3$, 600 MHz): δ = 7.28–7.22 (m, 3H), 7.11–7.10 (m, 2H), 5.75–5.68 (m, 1H), 5.17–5.15 (m, 2H), 4.24–4.14 (m, 2H), 3.25 (d, *J* = 13.8 Hz, 1H), 3.16 (d, *J* = 14.4 Hz, 1H), 2.59 (d, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 204.3, 171.5, 136.3, 132.4, 130.0, 128.3, 126.9, 119.3, 64.7, 61.4, 37.6, 36.1, 27.5, 14.0. HRMS (ESI) for $C_{16}H_{20}O_3Na$ $[M+H]^+$ calculated: 283.1310, found: 283.1318.

4.11.1. Bioreduction of compound 46

Bioreduction of compound **54** with *K. pneumoniae* (NBRC 3319) was carried out as described above for the synthesis of compounds **17**–**32**, to give inseparable mixture of compounds **48**/**50** (70%) as a colourless liquid.

4.12. Ethyl 2-benzyl-2-((*S*)-1-hydroxyethyl)pent-4-enoate 48/50

R_f = 0.3 (EtOAc/hexane, 1:10). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.26–7.12 (m, 5H), 6.02–5.76 (m, 1H), 5.17–5.08 (m, 2H), 4.19–3.86 (m, 3H), 3.29–3.05 (m, 2H), 2.94–2.74 (m, 1H), 2.62–2.54 (m, 1H), 2.42–2.32 (m, 1H), 1.28–1.08 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 176.1, 175.7, 137.4, 137.3, 134.5, 134.3, 130.4, 130.1, 128.2, 128.1, 126.7, 126.6, 118.3, 70.7, 69.8, 60.9, 60.8, 55.3, 54.8, 39.6, 37.9, 36.9, 35.8, 18.5, 17.8, 14.2, 14.0. HRMS (ESI) for $C_{16}H_{22}O_3Na$ $[M+H]^+$ calculated: 285.1467, found: 285.1461.

4.13. Ethyl 2-benzyl-2-((*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl) pent-4-enoate (TBS protected)

Prepared in 84% yield as colourless oil analogous to the route described for **33** from the enantiopure secondary alcohol **48**/**50**. R_f = 0.6 (EtOAc/hexane, 1:20). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.25–7.17 (m, 5H), 6.09–5.75 (m, 1H), 5.08–4.92 (m, 2H), 4.21–4.05 (m, 3H), 3.15–2.71 (m, 2H), 2.53–2.31 (m, 2H), 1.23–0.88 (m, 15H), 0.07 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 174.7, 174.5, 138.2, 136.0, 135.4, 130.7, 130.5, 128.0, 126.4, 117.1, 116.4, 73.1, 72.9, 60.4, 60.3, 56.4, 56.1, 39.4, 39.3, 36.8, 34.7, 26.0, 25.9, 19.9, 19.1, 18.2, 18.1, 14.2, −3.6, −4.8, −4.8. HRMS (ESI) for $C_{22}H_{36}O_3SiNa$ $[M+H]^+$ calculated: 399.2331, found: 399.2337.

4.14. 2-Benzyl-2-((*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl)pent-4-en-1-ol 52/54

The reduction of the TBS protected ester compounds **48**/**50** was carried out as described above for the synthesis of compounds **51**/**53**. In this step the two diastereomers are separated by column chromatography.

4.14.1. (2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-2-phenethylbutan-1-ol 52

R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +22.2 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.38–7.20 (m, 5H), 6.03–5.82 (m, 1H), 5.16–5.02 (m, 2H), 3.89 (q, *J* = 6.4 Hz, 1H), 3.75–3.64 (m, 2H), 3.38 (d, *J* = 13.4 Hz, 1H), 3.22–3.12 (m, 1H), 2.43 (d, *J* = 13.4 Hz, 1H), 1.88–1.77 (m, 1H), 1.60–1.53 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 138.3, 133.5, 131.1, 128.1, 126.2, 118.3, 75.9, 64.8, 45.0, 37.3, 35.2, 26.0, 18.2, 18.1, −3.9, −4.9. HRMS (ESI) for $C_{20}H_{34}O_3SiNa$ $[M+H]^+$ calculated: 357.2226, found: 357.2221.

4.14.2. (2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-2-phenethylbutan-1-ol 54

R_f = 0.27 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +4.8 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.26–7.25 (m, 5H), 5.97–5.76 (m, 1H), 5.13–5.07 (m, 2H), 3.94 (q, *J* = 6.2 Hz, 1H), 3.68–3.46 (m, 2H), 2.92 (t, *J* = 5.6 Hz, 1H), 2.79 (d, *J* = 13.6 Hz, 1H), 2.41 (d, *J* = 13.6 Hz, 1H), 2.31–2.07 (m, 2H), 1.29 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 138.1, 134.9, 130.9, 128.2, 126.4, 118.1, 74.3, 66.9, 45.5, 36.7, 36.5, 26.1, 18.6, 18.2, −3.6, −4.8. HRMS (ESI) for $C_{20}H_{34}O_3SiNa$ $[M+H]^+$ calculated: 357.2226, found: 357.2221.

4.15. 3-Benzyl-3-((*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl)hex-5-en-2-one 56/58

Prepared in 90% yield as colourless oil analogous to the route described above for the synthesis of **55**/**57**.

4.15.1. (3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-phenethylpentan-2-one 56

R_f = 0.6 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +44.2 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.26–7.07 (m, 5H), 5.89–5.69 (m, 1H), 5.05–4.95 (m, 2H), 4.06 (q, *J* = 6.4 Hz, 1H), 3.37 (d, *J* = 14.4 Hz, 1H), 2.73 (d, *J* = 14.4 Hz, 1H), 2.42–2.26 (m, 5H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 212.2, 137.8, 135.0, 130.1, 128.4, 126.6, 117.7, 72.7, 60.4, 39.0, 35.2, 29.8, 26.1, 19.2, 18.2, −3.7, −4.8. HRMS (ESI) for $C_{21}H_{34}O_2SiNa$ $[M+H]^+$ calculated: 369.2226, found: 369.2219.

4.15.2. (3*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-phenethylpentan-2-one 58

R_f = 0.56 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +22.6 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.22–7.10 (m, 5H), 5.92–5.79 (m, 1H), 5.06–4.98 (m, 2H), 4.03 (q, *J* = 6.4 Hz, 1H), 3.39 (d, *J* = 14.4 Hz, 1H), 2.75 (d, *J* = 14.4 Hz, 1H), 2.40–2.28 (m, 5H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 212.2, 137.8, 135.0, 130.1, 128.4, 126.6, 117.7, 72.7, 60.4, 39.0, 35.2, 29.8, 26.1, 19.2, 18.2, −3.7, −4.8. HRMS (ESI) for $C_{21}H_{34}O_2SiNa$ $[M+H]^+$ calculated: 369.2226, found: 369.2222.

4.16. 3-Benzyl-3-((*S*)-1-hydroxyethyl)hex-5-en-2-one 60/62

The deprotection of TBS group was carried out as described above for the general procedure of TBS deprotection of compounds **41**–**44**.

4.16.1. (3*R*,4*S*)-4-Hydroxy-3-methyl-3-phenethylpentan-2-one 60

R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +12.6 (*c* 0.6, $CHCl_3$).

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.26–7.21 (m, 3H), 7.11–7.07 (m, 2H), 5.89–5.69 (m, 1H), 5.05–4.95 (m, 2H), 4.06 (q, *J* = 6.4 Hz, 1H),

3.37 (d, J = 14.4 Hz, 1H), 2.73 (d, J = 14.4 Hz, 1H), 2.42–2.26 (m, 5H), 1.12 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 212.2, 137.8, 135.0, 130.1, 128.4, 126.6, 117.7, 72.7, 60.4, 39.0, 35.2, 29.8, 19.1. HRMS (ESI) for $C_{15}H_{20}O_2Na$ $[M+H]^+$ calculated: 255.1361, found: 255.1364.

4.16.2. (3*S*,4*S*)-4-Hydroxy-3-methyl-3-phenethylpentan-2-one 62

R_f = 0.27 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +5.8 (c 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.26–7.18 (m, 3H), 7.10–7.05 (m, 2H), 5.88–5.64 (m, 1H), 5.05–4.97 (m, 2H), 4.04 (q, J = 6.4 Hz, 1H), 3.38 (d, J = 14.4 Hz, 1H), 2.75 (d, J = 14.4 Hz, 1H), 2.40–2.28 (m, 5H), 1.15 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 212.4, 137.6, 135.2, 130.0, 128.7, 126.5, 117.2, 72.8, 60.6, 39.2, 35.1, 29.6, 19.0. HRMS (ESI) for $C_{15}H_{20}O_2Na$ $[M+H]^+$ calculated: 255.1361, found: 255.1366.

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