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Enantioselective synthesis of unsaturated α-hydroxy acids †

Jacqueline A. Macritchie,[b] Alan Silcock[a] and Christine L. Willis[a,*]

[a] School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK
[b] AgrEvo UK Ltd, Chesterford Park, Saffron Walden, Essex, CB10 1X2, UK

Abstract: (*S*)- and (*R*)-2-Hydroxyhex-5-enoic acid and (*S*)- and (*R*)-2-hydroxyhept-6-enoic acid were prepared in excellent yields and enantiomeric excesses (>99% ee) from the corresponding α-keto esters by the enzyme catalysed hydrolysis of the ester and reduction of the ketone in a single pot process. The enantioselective synthesis of (*S*)-2-hydroxypent-4-enoic acid was achieved via reaction of the reagent derived from allyl bromide and indium metal with the hydrate of 8-phenylmenthyl glyoxalate in water. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Oxygen containing heterocycles including tetrahydrofurans, tetrahydropyrans as well as both γ- and δ-lactones are components of a diverse range of biologically important natural products. Many methods are known for their synthesis, but a common approach involves the intramolecular cyclisation of a carboxlate anion or hydroxyl group onto an an alkene or derivative thereof e.g. iodoetherifications, iodolactonisations, nucleophilic attack onto epoxides.[1] Therefore a strategy giving access to various enantioenriched unsaturated alcohols/acids, as precursors to these heterocycles, would be of widespread use. We now report our investigations on the synthesis and bioreductions of two novel unsaturated α-keto acids to give the corresponding (*R*)- and (*S*)-2-hydroxy acids and the preparation of (*S*)-2-hydroxypent-4-enoic acid using organoindium chemistry.

Results and discussion

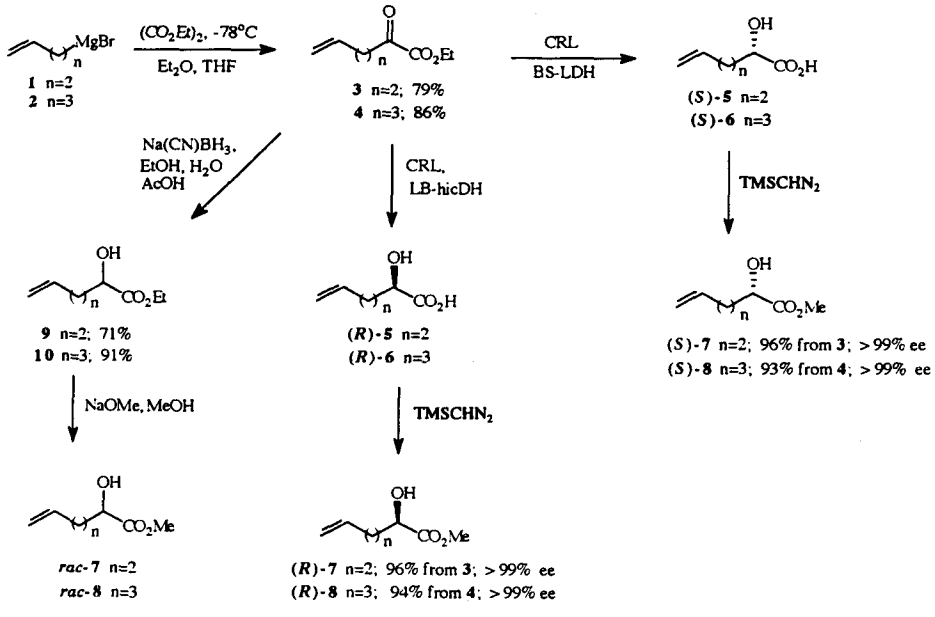
Preparation and bioreductions of unsaturated α-keto acids

Many methods are known for the synthesis of α-keto esters[2] and we favoured the use of a Grignard reaction for the preparation of our initial two target keto esters **3** and **4**. Treatment of but-3-enylmagnesium bromide **1** with diethyl oxalate at −78°C proceeded smoothly giving pure ethyl 2-oxohex-4-enoate **3** in 79% yield and under similar conditions, ethyl 2-oxohept-6-enoate **4** was prepared from pent-4-enylmagnesium bromide **2** in 86% yield (Scheme 1).

The next stage of the synthesis of the enantiopure alcohols required hydrolysis of the α-keto esters and stereoselective reduction of the analogous keto acids. The only enzyme catalysed reductions of unsaturated α-keto acids which have been reported previously are with β,γ-unsaturated-α-keto acids. For example, Bonnaffe and Simon[3] have used resting cells of *Proteus vulgaris* to reduce a series of (*E*)-2-oxo-5-alkoxypent-3-enoic acids to the corresponding (2*R*)-alcohols whilst Casy and coworkers[4] used L-lactate dehydrogenases to synthesise (*S*)-2-hydroxyalk-3-enoic acids from the analogous keto acids.

To prepare our target unsaturated (*S*)-2-hydroxy acids, we favoured the use of the commercially available lactate dehydrogenase from *Bacillus stearothermophilus* (BS-LDH) which is ideally suited as a synthetic catalyst as it is easy to handle (being thermostable) and has a reasonably broad substrate specificity range.[5] Lactate dehydrogenase from *Staphylococcus epidermis* (SE-LDH) has

† Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.
* Corresponding author.



Scheme 1.

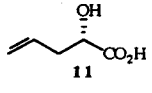
been widely used to catalyse the reduction of α-keto acids to (2*R*)-hydroxy acids.[6] However, we have found that although good yields of enantiopure products may be obtained using this catalyst, the reactions tend to be rather sluggish.[7] Hence we have investigated the use of D-2-hydroxy-4-methylvalerate dehydrogenase (also known as D-2-hydroxyisocaproate dehydrogenase[8]) from *Lactobacillus delbrueckii* subsp. *bulgaricus* (LB-hicDH) for which more favourable kinetic parameters have been reported recently.[9] Both BS-LDH and LB-hicDH require the co-factor NADH which may be recycled using a formate–formate dehydrogenase (FDH) protocol developed by Shaked and Whitesides[10] which allows the reactions to be performed economically on a multigram scale.

First it was necessary to convert the α-keto esters **3** and **4** to their corresponding carboxylic acids. This may be achieved by saponification with sodium hydroxide[11] but a more convenient method proved to be the use of a dual enzyme procedure to hydrolyse the ester and reduce the ketone in a one-pot process. For example, α-keto ester **3** was incubated with a lipase from *Candida rugosa* (CRL) prior to the addition of the dehydrogenases, BS-LDH and FDH and the requisite co-factors. After work up, (*S*)-2-hydroxyhept-6-enoic acid (*S*)-**5** was isolated and then methylated with trimethylsilyl diazomethane to give hydroxy ester (*S*)-**7** in 96% overall yield from **3**. The results from the hydrolyses and bioreductions of α-keto esters **3** and **4** are summarised in Scheme 1. Each α-keto ester was efficiently hydrolysed and then the ketone reduced giving the corresponding (*S*)- and (*R*)- hydroxy acids in excellent yields.

To determine the enantiomeric purity of the products from the enzyme catalysed reductions it was first necessary to prepare the racemic alcohols. Reduction of ethyl 2-oxohex-5-enoate **3** and ethyl 2-oxo-hept-6-enoate **4** with sodium cyanoborohydride proceeded smoothly giving **9** and **10** in 71% and 91% yields respectively. The ethyl esters were then transesterified to the required racemic methyl esters *rac*-**7** and *rac*-**8**. ^{1}H-, ^{13}C- and ^{19}F-NMR analysis of the (*R*)-MTPA (Mosher[12]) derivatives of the hydroxy esters were used to determine the enantiomeric purity of each product from the enzyme catalysed reductions, and was found to be uniformly high (>99% ee). In each case, chemical shift differences between diastereomers were entirely consistent with the expected absolute configuration at C-2 according to correlation models of Mosher[12] and Yamaguchi.[13]

Preparation of (S)-2-hydroxypent-4-enoic acid 11

Initially it was planned to prepare ethyl 2-oxopent-4-enoate **12** via a Grignard reaction, then hydrolysis and enzyme catalysed reduction would extend the above series and enable the synthesis of (*S*)-2-hydroxypent-4-enoic acid **11**. We had anticipated that there may be a problem with this approach insomuch that the double bond may migrate into conjugation giving ethyl 2-oxopent-3-enoate.[14] However, we found that treatment of allylmagnesium bromide with diethyl oxalate at −78°C gave a complex mixture of products from which only one compound was successfully isolated. The ^{13}C-NMR spectrum showed a single carbonyl resonance (δ 158) assigned to the ester but the characteristic signal usually assigned to the ketone of an α-keto ester (δ 190–δ 195) was absent. The IR spectrum showed a broad OH stretch at 3548 cm^{-1} and all other spectral data were consistent with the tertiary alcohol **13**. Interestingly, on reaction of ethyl oxalyl chloride and the organometallic reagent derived either from allyl chloride (or bromide)/magnesium/cuprous bromide/lithium bromide[15] or from allyl chloride/zinc[16], a single product **14** was obtained in excellent yield (90% and 95% respectively) arising from reaction of alcohol **13** with excess oxalate. Creary has reported that, during the reaction of a Grignard reagent with diethyl oxalate, the ester stabilises the magnesium salt of the tetrahedral adduct and the ketone is in fact not formed until hydrolytic work-up.[17] One plausible explanation for our unexpected results is that, following addition of the first allyl group, a further intramolecular attack of a metal co-ordinated allyl system via a 6-membered ring intermediate may occur to displace ethoxide giving the bis addition product **13**. This mechanism merits further investigation.



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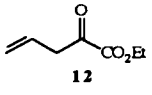

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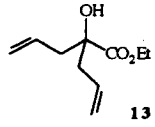

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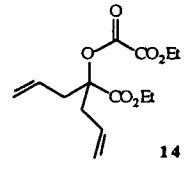

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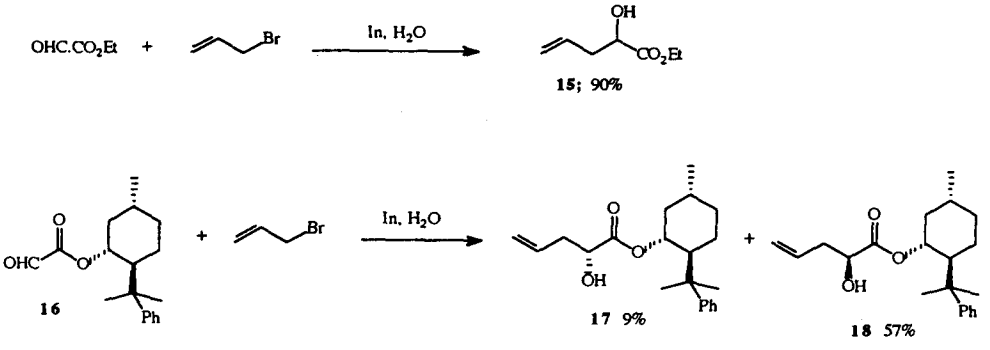
From the above results, it is clear that the approach used for the synthesis of the enantioenriched unsaturated α-hydroxy acids **5** and **6** is not viable for the synthesis of γ,δ-unsaturated α-hydroxy acid **11**. Although our efforts to use an enzyme catalysed reduction to create the asymmetric centre at C-2 of **11** were thwarted, we still favoured aqueous reaction conditions to achieve this transformation. Following the work of Whitesell *et al.*,[18,19] Dauben and coworkers[20] reported the synthesis of (*S*)-2-hydroxypent-4-enoic acid **11** by the $SnCl_4$ catalysed ene reaction between 8-phenylmenthyl glyoxalate **16** and propene to give **18** followed by hydrolytic cleavage of the chiral auxiliary. Excellent diastereoselectivity was achieved in this reaction, but drying the glyoxalate was problematic. To overcome this problem, we have explored the addition of the organoindium reagent derived from allyl bromide and indium metal in water[21] to the hydrate of glyoxalate **16** for the preparation of **11**. First the reaction conditions were optimised using ethyl glyoxalate as the electrophile and a pleasing 90% yield of racemic α-hydroxy ester **15** was obtained (Scheme 2).

We then prepared the hydrate of aldehyde **16** following a literature procedure via ozonolysis of 8-phenylmenthylacrylate.[19] Treatment of **16** with allyl bromide in the presence of indium in water gave **18** as the major product (a known precursor to the required unsaturated (*S*)-hydroxy acid **11**)[20] and a minor amount of the diastereomer **17** which were separable by flash chromatography.

In conclusion, a simple and efficient method has been developed for the synthesis of enantiopure unsaturated α-hydroxy carboxylic acids **5** and **6** from α-keto esters **3** and **4** based on the use of two enzyme catalysed transformations conducted in a one-pot process. Due to problems associated with the preparation of ethyl 2-oxopent-4-enoate **12**, an alternative approach for the synthesis of 2-hydroxypent-4-enoic acid **11** was investigated. Treatment of the hydrate of 8-phenylmenthyl glyoxalate with an organoindium reagent under aqueous conditions gave access to enantiopure (*S*)-2-hydroxypent-4-enoic acid via **18** in good yield.



Scheme 2.

Experimental section

NMR spectra were recorded as solutions in $CDCl_3$ unless stated otherwise, using tetramethylsilane as the internal reference. The spectra were recorded on a Jeol Lambda 300 MHz spectrometer. Mass spectra were recorded on a VG Analytical Autospec. and electrospray mass spectra on a VG Quattro Quadrupole mass spectrometer with EI source. IR spectra were recorded on a Perkin–Elmer 197 spectrophotometer as neat solutions on sodium chloride plates. Routine analytical thin layer chromatography was performed on Merck DC-Alufolien Kieselgel 60 F_{254} aluminium backed plates. The plates were developed with the appropriate solvent system and visualised either by a Mineralight UV lamp using a $KMnO_4$ dip {$KMnO_4$ (3 g), K_2CO_3 (20 g), 5% NaOH (5 ml) in H_2O (300 ml)}. Flash column chromatography was carried out with Merck Kieselgel 60 silica gel eluting with ethyl acetate–petroleum ether. Optical rotations were determined as solutions in $CHCl_3$, irradiation with sodium D line 589 nm using a Perkin–Elmer 241 MC polarimeter.

Enzymes were obtained from the following: lipase from *Candida rugosa* (CRL)-Sigma; protein (100,00 eU) dissolved in phosphate buffer (100 ml, 5 mM) and stored at 4°C; FDH from *Candida boidinii*-Boerhinger, stored at 4°C; BS-LDH from *Bacillus stearothermophilus* (BS-LDH)-Genzyme stored at −20°C; LB-hic-DH from *Lactobacillus delbrueckii* subsp. *bulgaricus* (H205Q),[22] (a gift from Professor Holbrook, Department of Biochemistry, University of Bristol), stored at 4°C.

General procedure for the reaction of Grignard reagents with diethyl oxalate

To a dry flask containing magnesium (5.0 g, 208 mmol) was added a solution of the unsaturated halide (88.6 mmol) in THF (80 ml) dropwise with vigorous agitation. The resultant solution was then added dropwise to a mixture of diethyl oxalate (10 ml, 73.6 mmol), THF (50 ml) and ether (100 ml) at −78°C and the solution stirred for 4 h. The reaction was quenched by the addition of saturated ammonium chloride solution (100 ml) and the mixture then partitioned with ethyl acetate (3×100 ml). The organic phases were combined, dried over sodium sulfate and the solvent removed *in vacuo* to give the product which was purified by distillation or flash chromatography.

Ethyl 2-oxohex-5-enoate 3

Pale yellow liquid (bp 114°C at 40 mm Hg), 79% yield; (Found: MH^+, 157.0859. $C_8H_{12}O_3$ requires MH^+, 157.0865); υ_{max}/cm^{-1} 1741, 1730, 1682; δ_H 1.37 (3H, t, *J* 7, CH_3), 2.39 (2H, m, 4-H_2), 2.95 (2H, t, *J* 7, 3-H_2), 4.32 (2H, q, *J* 7, OCH_2), 5.03 (2H, m 6-H_2), 5.87 (1H, ddt, *J* 17, 10, 7, 5-H); δ_C 13.8 (CH_3), 26.8 (C-4), 38.2 (C-3), 62.3 (OCH_2), 115.7 (C-6), 136.0 (C-5), 160.9 (C-1), 193.6 (C-2); m/z (CI) 156 (M^+, 22%), 139 (7), 111 (10), 83 (100) and 55 (34).

Ethyl 2-oxohept-6-enoate 4

Pale yellow liquid (bp 118°C at 25 mm Hg), 86% yield; (Found: MH^+, 171.1018. $C_9H_{14}O_3$ requires MH^+, 171.1021); υ_{max}/cm^{-1} 1737 (br.), 1641; δ_H 1.31 (3H, t *J* 7, CH_3), 1.69 (2H, pent, *J* 7, 4-H_2), 2.05 (2H, m, 5-H_2), 2.79 (2H, t, *J* 7, 3-H_2), 4.26 (2H, q, *J* 7, OCH_2), 4.96 (2H, m, 7-H_2), 5.71 (1H, ddt, *J* 17, 10, 7, 6-H); δ_C 13.9 (CH_3), 22.0 (C-4), 32.7 (C-5), 38.3 (C-3), 62.3 (OCH_2), 115.5 (C-7), 137.4 (C-6), 161.1 (C-1), 194.4 (C-2); m/z (CI) 171 (MH^+, 4%), 141 (6), 97 (100) and 69 (72).

General method for hydrolysis and in situ *reduction of α-keto esters by CRL and a dehydrogenase*

α-Keto ester (3 mmol) was dissolved in methanol (6 ml) and the solution then diluted with TRIS buffer (90 ml, 5 mM solution) and sodium formate (2 equivalents) added. CR lipase (1 ml, 10,000 U) was added and the pH of the reaction maintained at ~8.0 by the addition of 2 M sodium hydroxide solution. When no further pH change was observed the solution was deoxygenated with nitrogen gas and FDH (10 mg), NADH (10 mg), LDH (10 mg or 1 ml for suspended solutions) and dithiothreitol (DTT, 2 ml, 1 M solution) added. The pH of the reaction was then maintained at ~6.5 by the addition of 2 M HCl. When no further pH change was observed the solution was acidified to pH 2.5 and concentrated *in vacuo*. The mixture was then partitioned with ethyl acetate, the organic phases combined, dried over sodium sulfate and concentrated *in vacuo*. The resultant α-hydroxy acid was then methylated with trimethylsilyl diazomethane and purified by column chromatography.

Methyl (R)-2-hydroxyhex-5-enoate (R)-7

Oil, 96% yield; $[\alpha]_D$ −16.3 (c 1.50 in $CHCl_3$); (Found: MH^+, 145.0865. $C_7H_{12}O_3$ requires MH^+, 145.0868); υ_{max}/cm^{-1} 3528, 1737, 1642; δ_H 1.63 (2H, m, 3-H_2), 2.05 (2H, m, 4-H_2), 3.57 (3H, s, OCH_3), 4.05 (1H, dd, *J* 8, 4, 2-H), 4.87 (2H, m, 6-H_2), 5.77 (1H, ddt, *J* 17, 10, 7, 5-H); δ_C 28.9 (C-3), 33.4 (C-4), 52.4 (OCH_3), 69.7 (C-2), 115.4 (C-6), 137.3 (C-5), 175.6 (C-1); m/z (CI) 145 (MH^+, 90%), 127 (52), 113 (28) and 85 (100).

Methyl (S)-2-hydroxyhex-5-enoate (S)-7

Oil, 96% yield; $[\alpha]_D$ +18 (c 1.5 in $CHCl_3$); spectroscopic data as for (*R*)-**7**.

Methyl (R)-2-hydroxyhept-6-enoate (R)-8

Oil, 94% yield; $[\alpha]_D$ −9.2 (c 1.52 in $CHCl_3$); (Found: MH^+, 159.1017. $C_8H_{14}O_3$ requires MH^+, 159.1021); υ_{max}/cm^{-1} 3446, 1741, 1641; δ_H 1.49–2.15 (6H, complex m, 3-H_2, 4-H_2 and 5-H_2), 2.66 (1H, br. s, OH), 3.79 (3H, s, OCH_3), 4.20 (1H, dd, *J* 7, 4, 2-H), 4.97 (1H, ddt, *J* 10, 2, 1, 7-*H*H), 5.02 (1H, dq, *J* 17, 2, 7-H*H*), 5.80 (1H, ddt, *J* 17, 10, 7, 6-H); δ_C 24.0 (C-4), 33.3 and 33.8 (C-3 and C-5), 52.5 (OCH_3), 70.3 (C-2), 114.9 (C-7), 138.2 (C-6), 175.8 (C-1); m/z (CI) 159 (MH^+, 24%) and 100 (100).

Methyl (S)-2-hydroxyhept-6-enoate (S)-8

Pale yellow oil, 93% yield; $[\alpha]_D$ +9.1 (c 1.57 in $CHCl_3$); spectroscopic data as for (*R*)-**8**.

General procedure for reduction of α-keto ester with sodium cyanoborohydride

Sodium cyanoborohydride (0.40 g, 6.4 mmol) was added to a solution of the α-keto ester (6.4 mmol) in a mixture of ethanol (30 ml), water (10 ml) and acetic acid (4 ml). The mixture was stirred at room temperature for 1 h. The solution was then acidified to pH 1 with 2 M HCl and the solution concentrated *in vacuo*. The mixture was partitioned with ethyl acetate (3×50 ml), the organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by column chromatography, eluting with ethyl acetate in 40–60 petrol, to give the 2-hydroxy ethyl ester. Transesterification to the methyl ester was carried out by stirring the ethyl ester in sodium methoxide/methanol for 12 hours at room temperature followed by the same work-up procedure reported above.

(±)-Ethyl 2-hydroxyhex-5-enoate ***9***

Colourless oil, 71% yield; (Found: MH^+, 159.1015. $C_8H_{14}O_3$ requires MH^+, 159.1021); υ_{max}/cm^{-1} 3431, 1740, 1642; δ_H 1.31 (3H, t, *J* 7, CH_3), 1.74 and 1.88 (each 1H, each m, 3-H_2), 2.18 (2H, m, 4-H_2), 2.71 (1H, br. s, OH), 4.19 (1H, dd, *J* 8, 4, 2-H), 4.25 (2H, q, *J* 7, OCH_2), 5.04 (2H, m, 6-H_2), 5.82 (1H, ddt, *J* 17, 10, 7, 5-H); δ_C 14.1 (CH_3), 28.9 and 33.5 (C-3 and C-4), 61.6 (OCH_2), 69.7 (C-2), 115.4 (C-6), 137.4 (C-5), 175.2 (C-1); m/z (CI) 159 (MH^+, 1%), 141 (MH^+ −18, 50%), 113 (82) and 84 (100).

(±)-Ethyl 2-hydroxyhept-6-enoate ***10***

Colourless oil, 91% yield; (Found: MH^+, 173.1176. $C_8H_{16}O_3$ requires MH^+, 173.1178); υ_{max}/cm^{-1} 3469, 1736, 1641; δ_H 1.30 (3H, t, *J* 7, CH_3), 1.46–1.85 (4H, m, 3-H_2 and 4-H_2), 2.09 (2H, m, 5-H_2), 2.82 (1H, br. s, OH), 4.18 (1H, dd, *J* 7, 4, 2-H), 4.25 (2H, q, *J* 7, OCH_2), 5.00 (2H, m, 7-H_2), 5.80 (1H, ddt, *J* 17, 10, 7, 6-H); δ_C 14.1 (CH_3), 24.0 (C-4), 33.3 and 33.7 (C-3 and C-5), 61.6 (OCH_2), 70.3 (C-2), 114.8 (C-7), 138.2 (C-6), 175.3 (C-1); m/z (CI) 173 (MH^+, 20%), 155 (48), 109 (40) and 81 (100).

General procedure for the formation of the Mosher ester derivatives

α-Hydroxy ester (~0.1 mmol) was dissolved in CH_2Cl_2 (2 ml) and a crystal of DMAP added. Anhydrous triethylamine (3 eq.) was added, followed by (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (2 eq.) and the mixture stirred until complete by TLC (~1 h). The solution was then passed through a short pad of silica and washed through with 20% ethyl acetate in petroleum ether 40–60. The resulting solution was concentrated *in vacuo* to give the product which was analysed by ^1H-, ^{13}C- and ^{19}F-NMR spectroscopy.

- MTPA of *rac*-**7**: δ_H 3.57 (dq, *J* 1Hz, OCH_3), 3.65 (dq, *J* 1Hz, OCH_3), 3.75 (s, CO_2CH_3), 3.79 (s, CO_2CH_3); δ_F −71.53, −71.93.
- MTPA of (*R*)-**7**: δ_H 3.65 (dq, *J* 1Hz, OCH_3), 3.79 (s, CO_2CH_3); δ_F −71.53.
- MTPA of (*S*)-**7**: δ_H 3.57 (dq, *J* 1Hz, OCH_3), 3.75 (s, CO_2CH_3); δ_F −71.93.
- MTPA of *rac*-**8**: δ_H 3.56 (dq, *J* 1Hz, OCH_3), 3.65 (dq, *J* 1Hz, OCH_3), 3.75 (s, CO_2CH_3), 3.79 (s, CO_2CH_3): δ_F −71.60, −71.94.
- MTPA of (*R*)-**8**: δ_H 3.65 (dq, *J* 1Hz, OCH_3), 3.79 (s, CO_2CH_3); δ_F −71.60.
- MTPA of (*S*)-**8**: δ_H 3.56 (dq, *J* 1Hz, OCH_3), 3.75 (s, CO_2CH_3); δ_F −71.94.

Reaction of diethyl oxalate with allyl magnesium bromide

To a dry flask containing magnesium (0.78 g, 32.5 mmol) was added a solution of allyl bromide (2.4 ml, 27.8 mmol) in Et_2O (80 ml) dropwise with vigorous agitation under nitrogen. The resultant solution was then added dropwise to diethyl oxalate (1.9 ml, 13.9 mmol) in THF (30 ml) at −78°C and the solution stirred for 4 h. The reaction was quenched by the addition of saturated ammonium chloride solution (100 ml) and the mixture then partitioned with ethyl acetate (3×50 ml). The organic phases were combined, dried over sodium sulfate and the solvent removed *in vacuo* to give the product which was purified by flash chromatography to give ethyl 2-(prop-2′-ene)-2-hydroxypent-4-enoic acid **13** as a pale yellow oil (0.38 g, 19%); υ_{max}/cm^{-1} 3548, 1744, 1655; δ_H 1.39 (3H, t, *J* 7, CH_3), 2.44 (4H, dd, *J* 14, 7, 2×CH_2), 4.36 (2H, q, *J* 7, OCH_2), 5.12 (4H, m, 2×C=CH_2), 5.97 (2H, m, 2×C=CH); δ_C 13.8 (CH_3), 40.0 (C-3), 63.0 (OCH_2), 77.8 (C-2), 118.1 (2×C=CH_2), 134.6 (2×C=CH) and 157.8 (C-1); m/z (EI) 183 (M-1$^+$, 25%), 167 (45), 125 (25), 85 (70) and 69 (100).

Reaction of ethyl oxalyl chloride with allyl magnesium chloride in the presence of copper(I) bromide

Anhydrous copper bromide (2.4 g, 16.7 mmol) and anhydrous lithium bromide (2.9 g, 33.4 mmol) in THF (60 ml) at 0°C for 10 min. Allyl magnesium chloride (2 M in THF, 8.3 ml, 16.7 mmol) was added, followed by ethyl oxalyl chloride (1.6 ml, 13.9 mmol). The mixture was stirred for 2h at 0°C and then saturated ammonium chloride solution (50 ml) was added. The mixture was partitioned with ethyl acetate (3×50 ml), the organic phases combined, dried over anhydrous sodium sulfate and

concentrated *in vacuo*. The product was then filtered through a pad of Celite, washed through with chloroform and the solvent removed *in vacuo* giving ethyl 2-(pent-2′-enyl)-2-(ethyl oxalyl)pent-4-enoate **14** as a pale yellow oil (1.78 g, 90% yield); υ_{max}/cm^{-1} 1750 br, 1642; δ_H 1.27 (3H, t, *J* 7, CH_3), 1.38 (3H, t, *J* 7, CH_3), 2.80 (2H, ddt, *J* 9, 7, 1, 2×C*H*H), 2.83 (2H, ddt, *J* 9, 7, 1, 2×CH*H*), 4.22 (2H, q, *J* 7, OCH_2), 4.35 (2H, q, *J* 7, OCH_2), 5.14 (4H, m, 2×H_2C=C), 5,74 (2H, m, 2×C=CH); δ_C 13.8 (CH_3), 14.0 (CH_3), 38.3 (2×*C*H_2–CH), 61.7 (OCH_2), 63.1 (OCH_2), 84.8 (C-2), 120.1 (2×*C*H_2=CH), 130.1 (2×CH_2=*C*H), 156.2 (C=O), 157.3 (C=O) and 169.4 (C-11); m/z (electrospray, 5 V) 284.4 (M^+, 100%).

*(±)-Ethyl 2-hydroxypent-4-enoate **15***

To a slurry of indium powder 150 mesh (1.26 g, 11 mmol) in water (100 ml) was added ethyl glyoxalate, 50% solution in toluene (2.0 ml, 10 mmol) and allyl bromide (1.3 ml, 15 mmol) and the mixture stirred for 24 h. During this time a white solid was precipitated. Ethyl acetate (50 ml) was then added and the mixture stirred for 0.5 h. The mixture was partitioned with ethyl acetate (3×50 ml), the organic phases dried over sodium sulfate and concentrated *in vacuo* to give a pale yellow oil (1.9 g). The product was purified by column chromatography, eluting with 20% ethyl acetate in 40/60 petrol to give **15** as a pale straw coloured liquid (1.3 g, 90%), (data not given previously[21]); (Found: MH^+, 145.0865. $C_7H_{12}O_3$ requires MH, 145.0864); υ_{max}/cm^{-1} 3472, 1736 br, 1642; δ_H 1.28 (3H, t, *J* 7, CH_3), 2.43 (1H, dddt, *J* 14, 7, 5, 1, 3-*H*H), 2.59 (1H, dddt, *J* 14, 7, 6, 1, 3-H*H*), 2.83 (1H, d, *J* 6, OH), 4.21 (1H, dq, *J* 14, 7, OC*H*HCH_3), 4.23 (1H, td, *J* 6, 5, 2-H), 4.24 (1H, dq, *J* 14, 7, OCH*H*CH_3), 5.14 (2H, m, 5-H_2), 5.79 (1H, ddt, *J* 17, 10, 7, 4-H); δ_C 14.3 (CH_3), 38.7 (C-3), 61.7 (OCH_2), 70.0 (C-2), 118.7 (C-5), 132.6 (C-4), 174.5 (C-1); m/z (CI) 145 (MH^+, 20%) and 115 (100).

*Treatment of the hydrate of 8-phenylmenthyl glyoxalate **16** with allyl bromide/indium in water*

To a slurry of indium metal (0.15 g, 1.32 mmol) in water (10 ml) was added allyl bromide (0.104 ml, 1.8 mmol) and 8-phenylmenthyl glyoxalate **16** (0.373 g, 1.2 mmol) and the mixture stirred for 16 h at room temperature. Ethyl acetate (20 ml) was added and the mixture stirred for 0.5 h before being passed through a pad of Celite. The organic phase was separated and the aqueous phase partitioned with ethyl acetate. The organic phases were combined, dried over sodium sulfate and concentrated *in vacuo*. The mixture was purified by flash chromatography. Elution with 5% ethyl acetate in light petroleum gave the less polar, minor product **17** followed by the more polar, major product **18**.

(*R*)-Hydroxy ester **17**: colourless oil, (0.035 g, 9%); $[\alpha]_D$ −1.0 (c. 1.75 in $CHCl_3$); υ_{max}/cm^{-1} 3438, 1724, 1640, 1598; δ_H 0.88 (3H, d, *J* 8, CH_3), 1.21 (3H, s, CH_3), 1.32 (3H, s, CH_3), 0.86–2.28 (8H, m, 4 CH_2, 2 CH), 3.74 (1H, dd, *J* 7,4, 2-H), 4.90 (1H, td, *J* 11, 4, CH), 5.05 (2H, m, 5-H_2), 5.69 (1H, ddt, *J* 17, 10, 4, 4-H), 7.25 (5H, m, Ph); δ_C 21.7 (CH_3), 23.4 (CH_3), 26.4 (CH_2), 29.3 (CH_3), 31.3 (CH), 34.4 (CH_2), 37.6 (CH_2), 39.5 (CH_3CCH_3), 41.6 (CH_2), 49.9 (CH), 70.7 (C-2), 75.9 (CHO), 118.1 (C-5), 125.2, 125.3 128.4, 152.3 (aromatics), 133.0 (C-4), 172.3 (C-1); m/z (CI) 331 (M^+, 0.6%), 215 (30), 119 (100) and 105 (95).

*(S)-2-Hydroxy ester **18***

Colourless oil, (0.227 g, 57%); $[\alpha]_D$ −6.2 (c. 1.75 in $CHCl_3$), (no data given previously[20]); υ_{max}/cm^{-1} 3487, 1726, 1642, 1598; δ_H 0.87 (3H, d, *J* 6, CH_3), 1.19 (3H, s, CH_3), 1.29 (3H, s, CH_3), 0.88–2.16 (10H, m, 4 CH_2, 2 CH), 3.27 (1H, dd, *J* 6,4, 2-H), 4.85 (1H, td, *J* 11, 4, CH), 5.03 (2H, m, 5-H_2), 5.61 (1H, ddt, *J* 17, 10, 4, 4-H), 7.21 (5H, m, Ph); δ_C 21.8 (CH_3), 23.1 (CH_3), 26.3 (CH_2), 29.5 (CH_3), 31.3 (CH), 34.5 (CH_2), 38.2 (CH_2), 39.4 (CH_3CCH_3), 41.6 (CH_2), 50.3 (CH), 69.2 (C-2), 75.9 (CHO), 118.3 (C-5), 125.2, 125.3, 128.3, 151.8 (aromatics), 132.4 (C-4), 173.8 (C-1); m/z (CI) 331 (M^+, 0.04%), 215 (22), 199 (14), 119 (100) and 105 (96).

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