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Nitrile biotransformations for the synthesis of enantiomerically enriched Baylis–Hillman adducts

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Received 8th October 2002, Accepted 14th November 2002
First published as an Advance Article on the web 23rd December 2002

Catalysed by the nitrile hydratase/amidase-containing *Rhodococcus* sp. AJ270 cells, a number of β-aryl- and β-alkyl-β-hydroxy-α-methylenepropiononitriles (the Baylis–Hillman nitriles) **1** underwent hydrolysis under mild conditions to produce the corresponding enantiomerically enriched Baylis–Hillman amides **2** and acids **3**. The enantioselectivity of the biotransformations was strongly determined by the steric effect of the substituents at the β-position of the substrates. The protection of the free hydroxy of β-phenyl-β-hydroxy-α-methylenepropiononitrile **1a** by methylation led to the enhancement of enantiocontrol of the biohydrolysis.

Introduction

The reaction between electron-deficient alkenes and aldehydes catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO), well-known as the Baylis–Hillman reaction, provides a direct entry to synthetically versatile α-methylene-β-hydroxy carbonyl/nitrile compounds.[1,2] Despite its obvious utility, this base-catalyzed reaction, however, suffers from a few drawbacks. For example, the Baylis–Hillman reaction usually takes a very long period of time under atmospheric pressure and some electron-deficient alkenes do not effectively participate in the reaction.[1a] It has been reported that whist acrylonitrile undergoes the reaction readily under ambient conditions,[3] acrylamide appears unreactive.[1a] Furthermore, although the Baylis–Hillman reaction involves the generation of a stereogenic center, the study of asymmetric reactions has only met with mixed success so far.[1b,4] Using chiral auxiliaries such as the Oppolzer camphor sultam used recently by Leahy *et al.*[5] and a camphor-derived hydrazide developed later by Yang and Chen,[6] efficient stereoselective Baylis–Hillman reactions have been achieved towards a number of aliphatic aldehydes. However, both chiral auxiliary approaches showed low to no reactivity against α-branched aliphatic aldehydes and, particularly, aromatic aldehydes.[5,6] Moderate to excellent enantioselectivity has been reported from the biocatalytic resolution of the secondary alcohol of the Baylis–Hillman adducts.[7] From the practical point of view, almost no useful catalytic enantioselective Baylis–Hillman reaction has been reported.[1b,4]

Since the successful industrial production of acrylamide from the microbial hydration of acrylonitrile, there has been an increasing interest in biotransformations of nitriles.[8] It has been known for decades that biotransformations of nitriles proceed through either a direct transformation into the acids catalyzed by a nitrilase or the nitrile hydratase-catalyzed hydration to the amides followed by the hydrolysis to the acids by the action of an amidase.[8] Recent studies have also shown that nitrile-hydrolyzing enzymes and the amidases display enantiomeric discriminations against nitrile and amide substrates, respectively, and therefore enantioselective biotransformations of nitriles have drawn much attention in recent years.[8,9] Among the various nitrile-hydrolyzing microorganisms reported, *Rhodococcus* sp. AJ270, an isolate from a soil sample,[10] appears to be a robust and efficient nitrile hydratase/amidase-containing biocatalyst able to hydrolyze nitriles in chemo-,[11] regio-[12] and enantioselective[13] manners. Interest in the Baylis–Hillman reaction and in the understanding of enzymes' action and their synthetic potential led us to undertake the current study.

Our previous study has revealed an interesting *ortho*-substituent effect for the *Rhodococcus* sp. AJ270-catalysed hydrolysis of nitriles; the hydrolysis of acrylonitrile gave acrylic acid without accumulation of acrylamide while methacrylonitrile afforded a mixture of methacrylamide and methacrylic acid in a short incubation time.[11] We envisaged that by introducing a stereogenic center into the α-position of acrylonitrile, the Baylis–Hillman nitrile, for example, the biotransformation would give rise to the Baylis–Hillman amide. More importantly, the amidase would kinetically resolve the amide and therefore produce optically active Baylis–Hillman amide and acid. It should be noted that the biotransformation of the Baylis–Hillman nitriles differs greatly from those lipase-catalyzed kinetic resolution of the secondary alcohol of the Baylis–Hillman substrates,[7] because in our case the stereogenic center is remote from or β-positioned to the enzyme-reacting cyano and amido function groups. To our knowledge, there is no such study reported in literature.[14]

Results and discussion

We first examined the preparation of the Baylis–Hillman amide from the biotransformation of α-methylene-β-hydroxy-β-phenylpropiononitrile **1a**. As we expected, *Rhodococcus* sp. AJ270 efficiently converted **1a** into the racemic α-methylene-β-hydroxy-β-phenylpropionamide **2a** in 90% yield under very mild conditions.[1a] Complete hydrolysis could yield the racemic Baylis–Hillman acid **3a**, but it took weeks, which makes this approach synthetically impractical. The slower conversion of the amide **2a** as we anticipated, however, allowed us to study the stereochemistry of this biocatalytic reaction (Scheme 1).

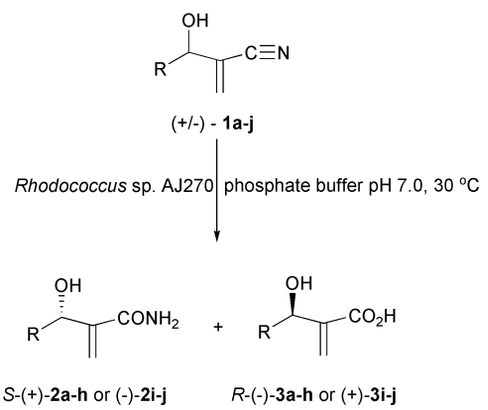
As shown in Table 1, biotransformations of racemic **1a** at around 50% conversion led to a kinetic resolution, yielding *S*-(+)-α-methylene-β-hydroxy-β-phenylpropionamide **2a** and *R*-(−)-α-methylene-β-hydroxy-β-phenylpropionic acid[14] **3a** with enantiomeric excesses ranging from 31–80% (entries 1 to 3 in Table 1). Complete hydrolysis of optically active *S*-(+)-α-methylene-β-hydroxy-β-phenylpropionamide **2a** (ee 63%) proceeded in 1 week with the aid of *Rhodococcus* sp. AJ270 to afford almost quantitatively *S*-(+)-α-methylene-β-hydroxy-β-phenylpropionic acid **4**[14] (ee 64%) (Scheme 2). The results indicated clearly that the nitrile hydratase involved in the microbial cells showed almost non-enantioselectivity against nitrile **1a** while the amidase exhibits *R*-enantioselection towards amide **2a**. To examine the substituent effect of the aromatic ring on the biotransformation reaction, a number of the Baylis–Hillman nitriles **1b–j** were prepared[7,15] and fed to *Rhodococcus* sp.

DOI: 10.1039/b209791e

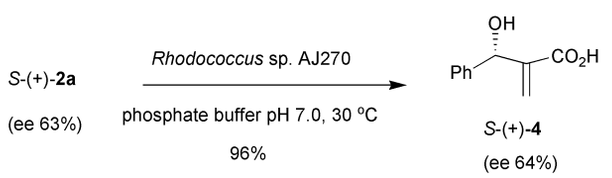
Table 1 Biotransformations of nitriles **1**

Entry	Substrate	Ar	Conditions[a]	**2**, yield (%)[b]	**2**, ee (%)[c]	**3**, yield (%)[b]	**3**, ee (%)[c]	E[d]
1	**1a**	C_6H_5	3 mmol, 24 h	90	0	—	—	—
2	**1a**	C_6H_5	1 mmol, 24 h	59	33	35	55	4.7
3	**1a**	C_6H_5	1 mmol, 36 h	46	63	47	45	4.8
4	**1a**	C_6H_5	1 mmol, 48 h	29	80	63	31	4.2
5	**1b**	4-MeO–C_6H_4	1 mmol, 24 h	43	41	52	27	2.5
6	**1c**	3-MeO–C_6H_4	1 mmol, 48 h	48	81	45	75	17
7	**1d**	2-MeO–C_6H_4	1 mmol, 72 h	50	79	44	70	13
8	**1e**	4-Me–C_6H_4	1 mmol, 72 h	45	41	45	45	3.9
9	**1f**	4-Cl–C_6H_4	0.5 mmol, 24 h	45	49	49	39	3.6
10	**1g**	3-Cl–C_6H_4	0.5 mmol, 48 h	49	53	45	38	3.6
11	**1h**	2-Cl–C_6H_4	0.5 mmol, 12 h	50	78	48	80	21
12	**1i**	Et	1 mmol, 45 min	44	0	47	0	—
13	**1j**	Me_2CH	3 mmol, 8 h	43	61	51	56	6.4
14	**1j**	Me_2CH	3 mmol, 10 h[e]	64	19	26	54	4.0

[a] The substrate was incubated with *Rhodococcus* sp. AJ270 cells (2 g wet weight) in phosphate buffer (pH 7.0, 10 mM, 50 ml). The reaction conditions were not optimized. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD or OJ column. [d] See ref. 17. [e] Acetone (3 ml) was added.



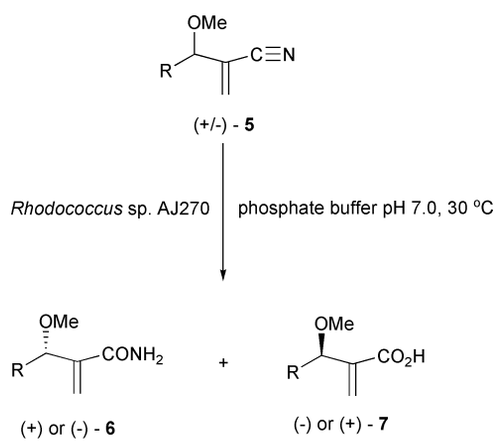
Scheme 1 Biotransformations of nitriles **1**.



Scheme 2 Bioconversion of *S*-(+)-amide **2a** into *S*-(+)-acid **4**.

AJ270. In all cases of nitriles **1b**–**h** derived from aromatic aldehydes, the reaction gave optically active *S*-(+)-amide **2b**–**h** and *R*-(−)-acid **3b**–**h**. It is interesting to note that, although the electronic nature of the substituent affected the enantiomeric excesses of the products, it was the substitution pattern that mainly governed the reaction enantioselectivity. For example, all substrates bearing a *para*-substituent such as **1d**, **1e** and **1h** resulted in modest enantioselectivity with enantiomeric ratio[16] E<4, whereas the *ortho*-substituted analogs **1b** and **1f** gave high enantioselectivity with E being 21 and 13, respectively. Good enantioselectivity (E 17) was also obtained for 3-methoxybenzaldehyde-derived Baylis–Hillman nitrile **1g**, but not for 3-chlorine substituted substrate **1c**. The highly preferential enantioselection for the *ortho*-substituted aromatic substrates in this study is intriguing, as for other α-substituted phenylacetonitriles and amides it is always the *para*-substitution on the aromatic ring that lead to the increase of enantioselectivity.[9,13] This may be due to the fact that in **1** or **2**, the aromatic ring is remote from or β-positioned to the cyano or amido functional group. The nitriles **1i**–**j** prepared form aliphatic aldehydes underwent a rapid hydrolysis under the similar reaction conditions. When the reaction was quenched at around 50% conversion of the amide, **1i** gave optically inactive products **2i** and **3i** in good yields while **1j** yielded (−)-**2j** and (+)-**3j** with moderate enantiomeric excesses (entries 12–14). The faster reaction and lower enantioselectivity of biotransformations of alkyl-containing Baylis–Hillman nitriles **1i** and **1j** in comparison to aryl-bearing nitriles **1a**–**h** suggested the sterically demanding nature of the enzymes.

To understand the role of the hydroxy group played in biotransformation, we protected it by methylation and the resulting substrate **5** was then subjected to biohydrolysis (Scheme 3). Compared to the reaction of the parent nitriles, the



Scheme 3 Biotransformations of *O*-methylated Baylis–Hillman nitriles

hydrolysis rate of all methyl protected nitriles **5** decreased. Intriguingly, however, the enantioselectivity of the reaction of **5a** was greatly enhanced, with E improving from 4.8 to 12, while the alkyl-substituted analogous substrates **5i** and **5j** did not give either improved or worsened enantiomeric excesses (Table 2). The outcomes suggest that it is the steric effect rather than the electronic or hydrogen bonding effect of the hydroxy substituent at stereogenic positions that determines the enantioselectivity of the enzymatic reaction. In other words, the biotransformation of analogous α,β-unsaturated nitriles bearing substituents other than hydroxy or alkoxy group would also take place in an enantioselective manner. Furthermore, this observation may open a new avenue to improve the enantioselective efficiency of the biotransformation of the Baylis–Hillman nitriles by masking the hydroxy using other protecting groups.[17]

In conclusion, we have shown that *Rhodococcus* sp. AJ270 is able to catalyze the hydrolysis of the Baylis–Hillman nitriles under mild conditions. Though the stereogenic center is remote or β-positioned to the cyano or amido functional group, the amidase involved in microbial cells still shows modest to good *R*-enantioselectivity. We have also found that the enantio-

Table 2 Biotransformations of nitriles **5**

Entry	Substrate	Ar	Conditions[a]	**6**, yield (%)[b]	**6**, ee (%)[c]	**7**, yield (%)[b]	**7**, ee (%)[c]	E[d]
1	**5a**	C_6H_5	1 mmol, 72 h	*S*-(+)-**6a** (47)	53	*R*-(−)-**7a** (43)	77	12
2	**5a**	C_6H_5	1 mmol, 168 h[e]	*S*-(+)-**6a** (57)	38	*R*-(−)-**7a** (34)	82	14
3	**5i**	Et	1 mmol, 7.5 h	(±)-**6i** (46)	0	(±)-**7i** (44)	0	—
4	**5j**	Me_2CH	1 mmol, 72 h	(−)-**6j** (47)	60	(+)-**7j** (44)	56	6.4

[a] The substrate was incubated with *Rhodococcus* sp. AJ270 cells (2 g wet weight) in phosphate buffer (pH 7.0, 10 mM, 50 ml). The reaction conditions were not optimized. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD or OJ column. [d] See ref. 17 [e] Acetone (2 ml) was added.

selectivity of the reaction is influenced by the steric factor of the substituent at the stereogenic center and it can be improved by engineering the Baylis–Hillman nitrile substrate with a methyl protection group at the hydroxy group. Our study has provided a new approach for the preparation of enantiomerically enriched R-(−)-β-aryl-β-hydroxy-α-methylenepropionic acids and their S-(+)-amides which are hardly accessible by other chemical[5,6] and enzymatic[7] methods. Biotransformation of various Baylis–Hillman nitriles and improvement of enantioselectivity utilizing protecting group strategy[17] is being actively studied in this laboratory.

Experimental

Both melting points, which were determined using a Reichert Kofler hot-stage apparatus, and boiling points are uncorrected. IR spectra were obtained on a Perkin-Elmer 782 instrument as liquid films or KBr discs. NMR spectra were recorded on Bruker AM 300 and Varian Unity 200 spectrometers. Chemical shifts are reported in ppm and coupling constants are given in hertz. Mass spectra were measured on an AEI MS-50 mass spectrometer and microanalyses were carried out by the Analytical Laboratory of the Institute.

Polarimetry was carried out using an Optical Activity AA-10R polarimeter and the measurements were made at the sodium D-line with a 5 cm pathlength cell. Concentrations (c) are given in g (100 ml)$^{-1}$. The enantiomeric excesses of all compounds were obtained with a Shimadzu LC-10AVP HPLC system, except for compounds **6i**,**j** and **7j** for which the enantiomeric excess values were determined by chiral GC analysis. Starting nitriles **1** were prepared according to the literature.[7,15]

General procedure for the preparation of *O*-methylated Baylis–Hillman nitriles 5

A mixture of the Baylis–Hillman nitrile **1** (10 mmol), methyl iodide (40 mmol) and Ag_2O (10 mmol) was stirred at room temperature for 24 h. Ether (30 ml) was added and the mixture was well stirred and filtered. After removal of the solvent, the residue was subjected to flash chromatography using a silica gel column with dichloromethane as the eluent.

3-Methoxy-2-methylene-3-phenylpropiononitrile 5a

(77%) was obtained as a colorless oil (Found: C, 75.89; H, 6.42; N, 8.42. $C_{11}H_{11}NO$ requires C, 75.89; H, 6.40; N, 8.09%); ν_{max}(KBr disc)/cm^{-1} 2226; δ_H(200 MHz; $CDCl_3$; Me_4Si) 7.37 (5 H, s), 6.01 (2 H, d, J 3.8), 4.75 (1 H, s) and 3.73 (3 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 57.0, 83.0, 116.8, 125.0, 126.9, 128.8, 130.8 and 137.3; m/z (EI) 173 (M^+, 4%), 142 (6) and 121 (100).

3-Methoxy-2-methylenepentanenitrile 5i

(60%) was obtained as a colorless oil; ν_{max}(KBr disc)/cm^{-1} 2225; δ_H(200 MHz; $CDCl_3$; Me_4Si) 6.09 (1 H, s), 5.94 (1 H, s), 3.62 (1 H, t, J 7.4), 3.34 (1 H, s), 1.83–1.67 (2 H, m) and 0.95 (3 H, t, J 7.4); δ_C(75 MHz; $CDCl_3$; Me_4Si) 9.3, 27.1, 56.8, 83.3, 116.7, 124.2 and 131.7; m/z (EI) 125 (M^+, 5%) and 96 (100).

3-Methoxy-4-methyl-2-methylenepentanenitrile 5j

(65%) was obtained as a colorless oil; ν_{max}(KBr disc)/cm^{-1} 2224; δ_H(200 MHz; $CDCl_3$; Me_4Si) 6.11 (1 H, s), 5.89 (1 H, s), 3.99 (1 H, s), 3.33 (3 H, s), 2.01–1.84 (1 H, m), 0.98 (3 H, J 7.2) and 0.92 (3 H, J 7.0); δ_C(75 MHz; $CDCl_3$; Me_4Si) 17.9, 18.6, 31.8, 57.3, 87.7, 117.0, 123.5 and 132.3; m/z (EI) 124 (M^+ − 15, 3) and 97 (100).

General procedure for the biotransformations of nitriles

To an Erlenmeyer flask (100 ml) with a screw cap were added *Rhodococcus* sp. AJ270 cells[10,11] (2 g wet weight) and potassium phosphate buffer (0.1 M, 50 ml) and the resting cells were activated at 30 °C for 30 min with orbital shaking. Racemic nitriles were added in one portion to the flask and the mixture was incubated at 30 °C with the use of an orbital shaker (200 rpm). The reaction, monitored by TLC, was quenched after a specified period of time (see Tables 1 and 2) by removing the biomass throughCelite pad filtration. The resulting aqueous solution was basified to pH 12 with aqueous NaOH (2 M). Extraction with ethyl acetate gave, after drying and concentration, the amides and unconverted nitriles. Separation of amide and nitrile was effected by column chromatography. The aqueous solution was then acidified using aqueous HCl (2 M) to pH 2 and extracted with ethyl acetate. Acid was obtained after removal of the solvent. All products were characterized by their spectral data and comparison of the melting points and optical rotary power with that of the known compounds or by full characterization.

Enzymatic hydrolysis of 3-hydroxy-2-methylene-3-phenylpropiononitrile 1a

3*S*-(+)-3-Hydroxy-2-methylene-3-phenylpropionamide **2a** (46%) was obtained as white solids (Found: C, 67.63; H, 6.21; N 8.07. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.90%); mp 94–96 °C; $[\alpha]_D^{25}$ +15.94 (c 1.38, CH_3OH); ee 63% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3380, 3185, 1660, 1630 and 1605; δ_H(200 MHz; DMSO-d_6; Me_4Si) 7.42 (1 H, s), 7.34–7.20 (5 H, m, Ar–H), 6.96 (1 H, s), 5.78 (1 H, s), 5.58 (1 H, s) and 5.48 (1 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 71.4, 117.8, 127.1, 127.4, 128.3, 143.6, 147.8 and 169.1; m/z (EI) 177 (M^+, 18%), 176 (46), 160 (21), 132 (30), 115 (19) and 105 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 28.6 min and t_- = 23.7 min.

3*R*-3-Hydroxy-2-methylene-3-phenylpropionic acid[14] **3a** (47%) was obtained as white solids (Found: C, 67.37; H, 5.72. $C_{10}H_{10}O_3$ requires C, 67.41; H, 5.66%); mp 80–81 °C (lit.[14] 79 °C); $[\alpha]_D^{25}$ −48.15 (c 0.5, CH_3OH) {lit.[14] $[\alpha]_D^{25}$ −23.2 (c 1.05, $CHCl_3$)}; ee 45% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2700–3352, 1686 and 1630; δ_H(200 MHz; $CDCl_3$; Me_4Si) 7.25–7.37 (5 H, m, Ar–H), 6.48 (1 H, s), 5.95 (1 H, s) and 5.56 (1 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 72.8, 126.7, 128.1, 128.5, 128.6, 140.8, 141.2 and 171.2; m/z (EI) 178 (M^+, 39%), 177 (39), 160 (13), 132 (43), 115 (29) and 105 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4(90:10:0.1) as the mobile phase

at a flow rate of 0.8 ml min^{-1} gave t_+ = 36.8 min and t_- = 20.8 min.

Enzymatic hydrolysis of 3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropiononitrile 1b

3*S*-(+)-3-Hydroxy-3-(4-methoxyphenyl)-2-methylenepropionamide **2b** (52%) was obtained as white solids (Found: C, 63.62; H, 6.21; N, 6.63. $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76%); mp 104–106 °C; $[a]_D^{25}$ +13.79 (*c* 1.0, CH_3OH); ee 41% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3379, 3181, 1659 and 1610; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.40 (1 H, s), 7.17 (2 H, d, *J* 8.7), 6.93 (1 H, s), 6.83 (2 H, d, *J* 8.7), 5.74 (1 H, s), 5.56 (1 H, s), 5.41 (1 H, s), 3.70 (3 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 55.8, 71.4, 114.0, 117.7, 128.7, 135.9, 148.4, 159.0 and 169.5; *m*/*z* (EI) 207 (M^+, 7%), 206 (9), 190 (18), 189 (18), 146 (14) and 135 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 46.0 min and t_- = 57.0 min.

3*R*-(−)-3-Hydroxy-3-(4-methoxyphenyl)-2-methylenepropionic acid **3b** (43%) was obtained as white solids (Found: C, 63.50; H 5.81. $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81%); mp 88–89 °C; $[a]_D^{25}$ −27.98 (*c* 1.93 CH_3OH); ee 27% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2600–3278, 1691 and 1618; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.30 (2 H, d, *J* 8.7), 6.89 (2 H, d, *J* 8.7), 6.47 (1 H, s), 5.97 (1 H, s), 5.41 (1 H, s) and 3.81 (3 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 55.6, 72.7, 114.2, 128.3, 128.5, 133.4, 141.7, 159.7 and 171.1; *m*/*z* (EI) 208 (M^+, 13%), 190 (24), 162 (14) and 146 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 61.3 min and t_- = 42.3 min.

Enzymatic hydrolysis of 3-hydroxy-3-(3-methoxyphenyl)-2-methylenepropiononitrile 1c

3*S*-(+)-3-Hydroxy-3-(3-methoxyphenyl)-2-methylenepropionamide **2c** (48%) was obtained as white solids (Found: C, 64.01; H, 6.27; N, 6.74. $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76%); mp 93.5–94.5 °C; $[a]_D^{25}$ +12.96 (*c* 1.23, CH_3OH); ee 81% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3389, 3214, 1630 and 1599; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.41 (1 H, s), 7.18 (1 H, t, *J* 8.0), 6.95 (1 H, s), 6.85–6.74 (3 H, m), 5.75 (1 H, s), 5.70 (1 H, br s), 5.55 (1 H, s), 5.43 (1 H, s) and 3.85 (3 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 55.7, 71.6, 112.9, 113.2, 118.2, 119.8, 129.7, 145.6, 148.1, 159.8 and 169.5; *m*/*z* (EI) 207 (M^+, 11%), 206 (19), 190 (19), 189 (23), 188 (10), 187 (19), 185 (18), 162 (14), 160 (15) and 135 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 48.6 min and t_- = 36.8 min.

3*R*-(−)-3-Hydroxy-3-(4-methoxyphenyl)-2-methylenepropionic acid **3c** (45%) was obtained as an oil; $[a]_D^{25}$ −76.6 (*c* 0.23, CH_3OH); ee 75% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2750–3500, 1702 and 1601; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.27 (1 H, t, *J* 8.1), 7.26 (1 H, s), 6.96–6.83 (2 H, m), 6.49 (1 H, s), 5.96 (1 H, s), 5.55 (1 H, s) and 3.81 (3 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 55.2, 72.7, 112.2, 113.5, 119.0, 128.7, 129.6, 141.1, 142.5, 159.6 and 171.2; *m*/*z* (EI) 207.0664 ($C_{11}H_{12}O_4$ requires 207.0663), 190 (36), 162 (32) and 135 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 34.8 min and t_- = 26.7 min.

Enzymatic hydrolysis of 3-hydroxy-3-(2-methoxyphenyl)-2-methylenepropiononitrile 1d

3*S*-(+)-3-Hydroxy-3-(2-methoxyphenyl)-2-methylenepropionamide **2d** (50%) was obtained as white solids (Found: C, 63.65; H, 6.38; N, 6.63. $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76%); mp 156–156 °C; $[a]_D^{25}$ +54.24 (*c* 0.88, CH_3OH); ee 79% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3383, 3339, 1668, 1621 and 1612; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.43 (1 H, s), 7.26–7.19 (2 H, m), 6.95–6.87 (2 H, m), 5.76 (1 H, s), 5.73 (1 H, s), 5.28 (1 H, s) and 3.73 (3 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 56.1, 65.7, 111.5, 118.7, 120.8, 128.0, 129.1, 131.6, 147.7, 157.1 and 169.8; *m*/*z* (EI) 207 (M^+, 5%), 206 (17), 189 (22), 176 (15), 137 (45) and 135 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OB column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 26.9 min and t_- = 34.3 min.

3*R*-(−)-3-Hydroxy-3-(2-methoxyphenyl)-2-methylenepropionic acid **3d** (44%) was obtained as white solids; mp 81–82; $[a]_D^{25}$ −55.27 (*c* 2.75, CH_3OH); ee 70% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2750–3500 and 1703 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.34–7.26 (2 H, m), 7.00–6.89 (2 H, m), 6.46 (1 H, s), 5.86 (1 H, s), 5.82 (1 H, s) and 3.85 (3 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 55.4, 68.1, 110.6, 120.8, 127.7, 128.3, 128.6, 129.1, 140.6, 156.6 and 171.6; *m*/*z* (EI) 207.0665 ($C_{11}H_{12}O_4$ requires 207.0663), 190 (18), 162 (33), 147 (24), 137 (42) and 135 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OD column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 12.9 min and t_- = 16.1 min.

Enzymatic hydrolysis of 3-hydroxy-2-methylene-3-(4-methylphenyl)propiononitrile 1e

3*S*-(+)-3-Hydroxy-2-methylene-3-(4-methylphenyl)propionamide **2e** (45%) was obtained as white solids (Found: C, 68.83; H, 6.80; N, 7.28. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32%); mp 117–118 °C; $[a]_D^{25}$ +16.28 (*c* 0.86, CH_3OH); ee 41% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3393, 3191, 1659 and 1618; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.39 (1 H, s), 7.15 (2 H, d, *J* 7.8), 7.08 (2 H, d, *J* 7.8), 6.93 (1 H, s), 5.75 (1 H, s), 5.59 (1 H, br s), 5.55 (1 H, s), 5.42 (1 H, s) and 3.25 (3 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 21.5, 71.7, 118.0, 127.5, 129.3, 136.8, 140.9, 148.3 and 169.6; *m*/*z* (EI) 191 (M^+, 9%), 190 (26), 174 (18), 146 (19) and 119 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 27.5 min and t_- = 25.4 min.

3*R*-(−)-3-Hydroxy-2-methylene-3-(4-methylphenyl)propionic acid **3e** (45%) was obtained as white solids (Found: C, 68.61; H, 6.22. $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.29%); mp 91–92 °C; $[a]_D^{25}$ −55.71 (*c* 1.79, CH_3OH); ee 45% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2759–3394, 1716, 1673 and 1623; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.26 (2 H, d, *J* 7.8), 7.17 (2 H, d, *J* 7.8), 6.48 (1 H, s), 5.98 (1 H, s), 5.55 (1 H, s) and 2.35 (3 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.0, 72.5, 126.4, 128.2, 129.0, 137.6, 137.7, 141.1 and 171.1; *m*/*z* (EI) 192 (M^+, 21%), 177 (26), 174 (28), 159 (8), 146 (30), 130 (51), 129 (43), 128 (33) and 119 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 28.9 min and t_- = 17.7 min.

Enzymatic hydrolysis of 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropiononitrile 1f

3*S*-(+)-3-(4-Chlorophenyl)-3-hydroxy-2-methylenepropionamide **2f** (45%) was obtained as white solids (Found: C, 56.41; H, 5.02; N, 6.63%. $C_{10}H_{10}NO_2Cl$ requires C, 56.75; H, 4.76; N, 6.62%); mp 127–129 °C; $[a]_D^{25}$ +13.89 (*c* 0.72, CH_3OH); ee 49% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3390, 3200, 1660 and 1620; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.45 (1 H, s), 7.33 (2 H, d, *J* 8.6), 7.29 (2 H, d, *J* 8.6), 6.97 (1 H, s), 5.79 (1 H, s), 5.60 (1 H, s) and 5.46 (1 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 70.7, 118.0, 128.3, 129.0, 131.9, 142.7, 147.5 and 168.9; *m*/*z* (EI) 213 (10), 212 (28), 211 (M^+, 31%), 210 (82), 196 (14), 194 (45),

168 (25), 166 (76), 141 (50) and 139 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 28.3 min and t_- = 25.2 min.

3*R*-(−)-3-(4-Chlorophenyl)-3-hydroxy-2-methylenepropionic acid **3f** (49%) was obtained as an oil; $[\alpha]_D^{25}$ −26.67 (*c* 0.22, CH_3OH); ee 39% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2750–3500, 1703 and 1631; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.32 (4 H, s), 6.49 (1 H,s), 5.97 (1 H,s) and 5.54 (1 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 72.2, 128.1, 128.7, 128.9, 133.8, 139.3, 140.9 and 171.1; *m*/*z* (EI) 214 (7), 213 (11), 211.0170 ($C_{10}H_9O_3Cl$ requires 211.0167), 211 (25), 194 (18), 177 (8), 166 (39) and 139 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 17.0 min and t_- = 13.5 min.

Enzymatic hydrolysis of 3-(3-chlorophenyl)-3-hydroxy-2-methylenepropiononitrile 1g

3*S*-(+)-3-(3-Chlorophenyl)-3-hydroxy-2-methylenepropionamide **2g** (45%) was obtained as white solids (Found: C, 56.76; H, 4.78; N, 6.58. $C_{10}H_{10}NO_2Cl$ requires C, 56.75; H, 4.76; N, 6.62%); mp 103.5–104 °C; $[\alpha]_D^{25}$ +11.35 (*c* 0.7, CH_3OH); ee 53% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3358, 3280, 3163, 1683 and 1594; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.49 (1 H, s), 7.34–7.22 (4 H, m), 7.00 (1 H, s), 5.90 (1 H, br s), 5.85 (1 H, s), 5.63 (1 H, s) and 5.47 (1 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 70.8, 118.2, 125.9, 126.8, 127.3, 130.3, 133.1, 146.3, 147.2 and 168.8; *m*/*z* (EI) 213 (2), 212 (9), 211 (M^+, 7%), 210 (26), 193 (22), 166 (25), 141 (67) and 139 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 26.9 min and t_- = 23.5 min.

3*R*-(−)-3-(3-Chlorophenyl)-3-hydroxy-2-methylenepropionic acid **3g** (47%) was obtained as an oil; $[\alpha]_D^{25}$ −35.9 (*c* 1.56, CH_3OH); ee 38% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2750–3500 and1700; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.39 (1 H, br s), 7.29 (4 H, s), 6.52 (1 H, s), 5.99 (1 H, s) and 5.55 (1 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 72.5, 125.2, 127.1, 128.5, 129.5, 130.1, 134.7, 141.0, 143.2 and 171.3; *m*/*z* (EI) 214 (7), 213 (9), 211.0169 ($C_{10}H_9O_3Cl$ requires 211.0167), 211 (21), 194 (16), 177 (17), 168 (16), 166 (38), 141 (46) and 139 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OK column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.2 ml min^{-1} gave t_+ = 42.1 min and t_- = 46.9 min.

Enzymatic hydrolysis of 3-(2-chlorophenyl)-3-hydroxy-2-methylenepropiononitrile 1h

3*S*-(+)-3-(2-chlorophenyl)-3-hydroxy-2-methylenepropionamide **2h** (50%) was obtained as white solids (Found: C, 57.04; H, 4.70; N, 6.63. $C_{10}H_{10}NO_2Cl$ requires C, 56.75; H, 4.76; N, 6.62%); mp 128–130 °C; $[\alpha]_D^{25}$ +46.32 (*c* 0.95, CH_3OH); ee 78% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3313, 3200, 1672 and 1595; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.52 (1 H, s), 7.39–7.21 (4 H, m), 6.97 (1 H, s), 5.79 (2 H, s), 5.69 (1 H, br s) and 5.27 (1 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 67.8, 118.8, 127.2, 128.8, 129.1, 129.4, 132.7, 140.6, 146.6 and 169.0; *m*/*z* (EI) 212 (6), 211 (M^+, 3%), 210 (18), 193 (19), 176 (96), 174 (28), 143 (22), 141 (91), 139 (83) and 77 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 34.1 min and t_- = 38.5 min.

3*R*-(−)-3-(2-Chlorophenyl)-3-hydroxy-2-methylenepropionic acid **3h** (48%) was obtained as an oil; $[\alpha]_D^{25}$ −45.71 (*c* 0.35, CH_3OH); ee 80% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2750–3500 and 1702; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.59–7.26 (4 H, m), 6.49 (1 H, s), 6.00 (1 H, s) and 5.70 (1 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 69.1, 127.4, 128.4, 129.5, 129.8, 129.9, 133.2, 138.3, 140.4 and 171.6; *m*/*z* (EI) 214 (10), 213 (23), 211.0169 ($C_{10}H_9O_3Cl$ requires 211.0167), 211 (60), 177 (81), 159 (45), 141 (73), 139 (75), 131 (41) and 77 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 27.1 min and t_- = 13.8 min.

Enzymatic hydrolysis of 3-hydroxy-2-methylenepentanenitrile 1i

(±)-3-Hydroxy-2-methylenepentanamide **2i** (44%) was obtained as white solids (Found: C, 57.31; H, 8.51; N, 10.70. $C_6H_{11}NO_2$ requires C, 57.80; H, 8.58; N, 10.84%); mp 53–54 °C; $[\alpha]_D^{25}$ 0 (*c* 0.4, CH_3OH); ee 0% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3382, 3193, 1658, 1629 and 1604; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.47 (1 H, s), 7.03 (1 H, s), 5.69 (1 H, s), 5.46 (1 H, s), 4.93 (1 H, d, *J* 5.1), 4.26 (1 H, t, *J* 6.7), 1.58–1.28 (2 H, m) and 0.82 (3 H, t, *J* 7.4); δ_C(75 MHz; DMSO-d_6; Me_4Si) 10.3, 29.3, 70.5, 117.2, 148.3 and 169.7; *m*/*z* (EI) 100 (M^+ − 29, 100) and 83 (86). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 16.3 min and t_- = 14.6 min.

(±)-3-Hydroxy-2-methylenepentanoic acid **3i** (47%) was obtained as an oil; $[\alpha]_D^{25}$ 0 (*c* 1.55, CH_3OH); ee 0% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2500–3427, 1698 and 1629; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.28 (2 H, br s), 6.39 (1 H, s), 5.91 (1 H, s), 4.38 (1 H, t, *J* 6.6), 1.78–1.62 (2 H, m) and 0.95 (3 H, t, *J* 7.4); δ_C(75 MHz; $CDCl_3$; Me_4Si) 9.9, 28.8, 72.6, 127.4, 141.3 and 170.9; *m*/*z* (EI) 129.0557 ($C_6H_{10}O_3$ requires 129.0557), 112 (M^+ − 18, 12), 101 (45) and 83 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (100:2:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_1 = 33.0 min and t_2 = 37.0 min.

Enzymatic hydrolysis of 3-hydroxy-2-methylene-4-methylpentanenitrile 1j

(−)-3-Hydroxy-2-methylene-4-methylpentanamide **2j** (43%) was obtained as white solids (Found: C, 58.92; H, 8.86; N, 9.93. $C_7H_{13}NO_2$ requires C, 58.72; H, 9.15; N, 9.78%); mp 123–124 °C; $[\alpha]_D^{25}$ −10.17 (*c* 3.0, CH_3OH); ee 61% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3320, 3170, 1680 and 1610; δ_H(200 MHz; DMSO-d_6; Me_4Si) 7.41 (1 H, s), 6.95 (1 H, s), 5.70 (1 H, s) 5.42 (1 H, s), 4.81 (1 H, br s), 4.13 (1 H, d, *J* 4.8), 1.79–1.63 (1 H, m), 0.84 (3 H, d, *J* 6.6) and 0.77 (3 H, d, *J* 7.0); δ_C(75 MHz; DMSO-d_6; Me_4Si) 17.0, 20.0, 32.2, 74.2, 117.9, 147.7 and 170.1; *m*/*z* (EI) 125 (M^+ − 18, 8), 101 (43), 100 (100) and 83 (59). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 16.3 min and t_- = 14.6 min.

(+)-3-Hydroxy-2-methylene-4-methylpentanoic acid **3j** (51%) was obtained as white solids (Found: C, 58.20; H, 8.48; $C_7H_{12}O_3$ requires C, 58.32; H, 8.39%); $[\alpha]_D^{25}$ +1.6 (*c* 2.5, CH_3OH); ee 56% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2607–3348, 1678, 1681 and 1630; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.09 (1 H, br s), 6.44 (1 H, s), 5.90 (1 H, s), 4.13 (1 H, d, *J* 6.9), 1.98 (2 H, octet, *J* 6.8), 0.98 (3 H, d, *J* 6.7) and 0.91 (3 H, d, *J* 6.8); δ_C(75 MHz; $CDCl_3$; Me_4Si) 17.5, 19.5, 32.5, 77.4, 128.7, 140.5 and 171.4; *m*/*z* (EI) 126 (M^+ − 18, 5), 111 (5), 102 (67), 101 (74), 84 (96) and 83 (100). Chiral HPLC analysis of the racemic acid methyl ester using a Chiralcel OD column with a mixture of hexane and propan-2-ol (20:1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 7.0 min and t_- = 7.9 min.

Enzymatic hydrolysis of 3-methoxy-2-methylene-3-phenylpropiononitrile 5a

3*S*-(+)-3-Methoxy-2-methylene-3-phenylpropionamide **6a** (47%) was obtained as white solids (Found: C, 69.10; H, 6.87;

N, 7.29. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N 7.32%); mp 108–109 °C; $[a]_D^{25}$ +26.67 (*c* 0.6, CH_3OH); ee 53% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 3397, 3207, 1643 and 1594; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.45 (1 H, s), 7.34–7.25 (5 H, m), 6.99 (1 H, s), 5.84 (1 H, s), 5.50 (1 H, s), 5.12 (1 H, s) and 3.19 (3 H, s); δ_C(75 MHz; DMSO-d_6; Me_4Si) 56.6, 80.8, 118.0, 127.5, 127.8, 128.4, 140.1, 145.0 and 168.4; *m*/*z* (EI) 191 (M^+, 5%), 190 (13), 176 (23) and 121 (100). Chiral HPLC analysis of the racemic amide using a Chiralcel OD column with a mixture of hexane and propan-2-ol (90:10:) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 17.4 min and t_- = 14.8 min.

3*R*-(−)-3-Methoxy-2-methylene-3-phenylpropionic acid **7a** (43%) was obtained as white solids (Found: C, 68.61; H, 6.22. $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.29%); mp 53–54 °C; $[a]_D^{25}$ −107.91 (*c* 1.39, CH_3OH); ee 77% (HPLC analysis); ν_{max}(KBr disc)/cm^{-1} 2750–3500, 1699 and 1630; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.35–7.29 (5 H, m), 6.47 (1 H, s), 5.98 (1 H, s), 5.10 (1 H, s) and 3.35 (3 H, s); δ_C(75 MHz; $CDCl_3$; Me_4Si) 56.9, 80.5, 127.3, 127.4, 127.9, 128.2, 138.8, 140.2 and 170.8; *m*/*z* (EI) 192 (M^+, 24%), 191 (16), 177 (31), 159 (27), 146 (28) and 121 (100). Chiral HPLC analysis of the racemic acid using a Chiralcel OJ column with a mixture of hexane, propan-2-ol and H_3PO_4 (90:10:0.1) as the mobile phase at a flow rate of 0.8 ml min^{-1} gave t_+ = 24.2 min and t_- = 15.5 min.

Enzymatic hydrolysis of 3-methoxy-2-methylenepentanenitrile 5i

(±)-3-Methoxy-2-methylenepentanamide **6i** (46%) was obtained as white solids mp 32.5–33.5 °C; $[a]_D^{25}$ 0 (*c* 1.2, CH_3OH); ee 7% (GC analysis); ν_{max}(KBr disc)/cm^{-1} 3355, 3184, 1671 and 1605; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.49 (1 H, s), 7.10 (1 H, s), 5.84 (1 H, s), 5.41 (1 H, s), 3.96 (1 H, t, *J* 5.9), 3.17 (3 H, s), 1.62–1.37 (2 H, m) and 0.81 (3 H, t, *J* 7.4); δ_C(75 MHz; DMSO-d_6; Me_4Si) 9.9, 27.8, 56.4, 80.8, 118.5, 144.2 and 169.1; *m*/*z* (EI) 144.1019 ($C_7H_{13}NO_2$ requires 144.1019), 128 (10), 114 (26) and 96 (100). Chiral DC analysis of the racemic amide using a chiral acidic 750Z column, 10 psi, from 110 °C to 140 °C (0.5 °C min^{-1}) gave t_1 = 35.0 min and t_2 = 38.0 min.

(±)-3-Methoxy-2-methylenepentanoic acid **7i** (44%) was obtained as an oil; $[a]_D^{25}$ 0 (*c* 0.65, CH_3OH); ν_{max}(KBr disc)/cm^{-1} 2750–3100, 1698 and 1629; δ_H(300 MHz; $CDCl_3$; Me_4Si) 6.49 (1 H, s), 5.92 (1 H, s), 4.01 (1 H, t, *J* 5.8), 3.31 (1 H, s), 1.72–1.56 (2 H, m) and 0.93 (3 H, t, *J* 7.4); δ_C(75 MHz; $CDCl_3$; Me_4Si) 9.4, 28.2, 56.7, 80.3, 127.4, 139.5 and 171.4; *m*/*z* (EI) 143.0711 ($C_7H_{12}O_3$ requires 143.0714), 129 (6), 115 (85) and 83 (100).

Enzymatic hydrolysis of 3-methoxy-4-methyl-2-methylenepentanenitrile 5j

(−)-3-Methoxy-4-methyl-2-methylenepentanamide **6j** (47%) was obtained as an oil; $[a]_D^{25}$ −27.68 (*c* 0.65, CH_3OH); ee 60% (GC analysis); ν_{max}(KBr disc)/cm^{-1} 3419, 3194, 1673, 1624 and 1605; δ_H(300 MHz; DMSO-d_6; Me_4Si) 7.43 (1 H, s), 7.03 (1 H, s), 5.81 (1 H, s), 5.32 (1 H, s), 3.74 (1 H, d, *J* 5.7), 3.11 (3 H, s), 1.70 (1 H, octet, *J* 6.6), 0.78 (3 H, d, *J* 6.3) and 0.76 (3 H, d, *J* 6.4); δ_C(75 MHz; DMSO-d_6; Me_4Si) 18.1, 19.7, 32.6, 57.3, 85.4, 119.8, 143.8 and 169.9; *m*/*z* (EI) 158.1173 ($C_8H_{15}NO_2$ requires 158.1175), 142 (12), 125 (16), 114 (52) and 97 (100). Chiral GC analysis of the corresponding racemic acid methyl ester using a chiral acidic 750Z column, 14 psi at 80 °C gave t_+ = 10.9 min and t_- = 11.7 min.

(+)-3-Methoxy-4-methyl-2-methylenepentanoic acid **7j** (44%) was obtained as an oil; $[a]_D^{25}$ +26.67 (*c* 0.45, CH_3OH); ν_{max}(KBr disc)/cm^{-1} 2750–3100, 1698 and 1627; δ_H(300 MHz; $CDCl_3$; Me_4Si) 6.54 (1 H, s), 5.87 (1 H, s), 3.82 (1 H, d, *J* 5.9), 3.30 (3 H, s), 1.89 (1 H, octet, *J* 6.6), 0.93 (3 H, d, *J* 6.8) and 0.92 (3 H, d, *J* 6.7); δ_C(75 MHz; $CDCl_3$; Me_4Si) 17.2, 18.9, 32.4, 57.3, 84.8, 128.5, 138.5 and 171.3; *m*/*z* (EI) 157.0869 ($C_8H_{14}O_3$ requires 157.0870), 126 (5), 115 (90) and 83 (100). Chiral GC analysis of the racemic acid using a chiral acidic 750Z column, 10 psi from 110 °C to 140 °C (2 °C min^{-1}) gave t_+ = 34.0 min and t_- = 32.0 min.

Acknowledgements

We thank the Major Basic Research Development Program (No. G2000077506), the Ministry of Science and Technology of China (Grant No. 2002CCA03100), the National Science Foundation of China and the Chinese Academy of Sciences for financial Support. M.-X. W also thanks O. Meth-Cohn and J. Colby for discussion.

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