Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 265–273

TETRAHEDRON: *ASYMMETRY*

Chiral, non-racemic α-hydroxyphosphonates and phosphonic acids via stereoselective hydroxylation of diallyl benzylphosphonates

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Received 28 October 2002; accepted 20 November 2002

Abstract—Chiral, non-racemic α-hydroxyphosphonates have been prepared in high enantiomeric excess (96–98% ee), via stereoselective oxaziridine-mediated hydroxylation of diallyl benzylphosphonates. The enantiomeric purity and absolute configuration of the α-hydroxyphosphonates was established from ^{1}H and ^{31}P NMR spectroscopy of the (*S*)-*O*-methylmandelate esters. Deprotection of the diallyl α-hydroxyphosphonates under neutral conditions furnished the corresponding free phosphonic acids, retaining a high degree of stereochemical purity (90 to >98% ee).

1. Introduction

α-Hydroxyphosphoryl compounds are important bioactive molecules known to inhibit a range of enzymes. They are also attractive precursors to α-aminophosphoryl isosteres of α-amino acids. α-Hydroxyphosphonic acids are found to inhibit farnesyl protein transferase,[1] enolpyruvylshikimate-3-phosphate synthase,[2] tyrosine-specific protein kinase[3] and HIV protease,[4] whereas α-hydroxyphosphonate esters are found to inhibit renin angiotensin synthase.[5] Most bioactivity studies have been performed using either free phosphonic acids[1–3] or phosphonate diesters, however, those studies which have compared the activities of both, have often revealed a drastic difference in potency attributed to additional hydrogen bond formation of the free acid, or conversely, interaction of the ester groups with catalytic moieties in the active site of the enzyme.[4,5] Furthermore, although the absolute configuration at the α-centre has been shown to influence the biological properties of α-substituted phosphoryl compounds,[5] most bioactivity studies are performed employing racemic compounds.[1–4] We were interested in a simple and efficient stereoselective route that gives rise to both enantiomerically pure α-hydroxyphosphonates and their corresponding phosphonic acids, as key precursors in the asymmetric synthesis of potent sialyltransferase inhibitors,[6] and as an essential tool for further investigation into the role of α-hydroxyphosphoryl compounds in biological processes.

Chiral, non-racemic dialkyl α-hydroxyphosphonates have been prepared via several methods, as has been recently reviewed,[7,8] including chiral variations of either the Pudovik reaction[9] or the Abramov reaction,[10] chemical[11] or enzymatic resolution,[12] or employing catalytic asymmetric methods.[8] On the other hand, enantioenriched dialkyl α-hydroxyphosphonic acids have been prepared by enantioselective addition of aldehydes to chiral phosphorous acid diamides[13] followed by hydrolysis of the phosphonamides,[14] or more often by hydrolysis of the corresponding non-racemic α-hydroxyphosphonates prepared by one of the methods described above.

The majority of these stereoselective routes are aimed at the preparation of dialkyl α-hydroxyphosphonates,[7,8] and yet, unlike their related carboxylate esters, simple phosphonate dialkyl esters are not generally converted in vivo to their corresponding free acids.[15] For the majority of bioactivity studies, which require phosphonic acids, the harsh conditions necessary to liberate the free acid from the dialkyl ester form, may lead to substantial racemisation of the crucial, newly-formed, non-racemic α-centre.[11]

Since their introduction as easily removable phosphonate protecting groups,[16] diallyl phosphonate esters have been employed successfully in the synthesis of sialyltransferase inhibitors,[6,17] in the field of solid-phase peptide synthesis of phosphonic acid isosteres of α-amino acids[18] and also in the synthesis of α,α-

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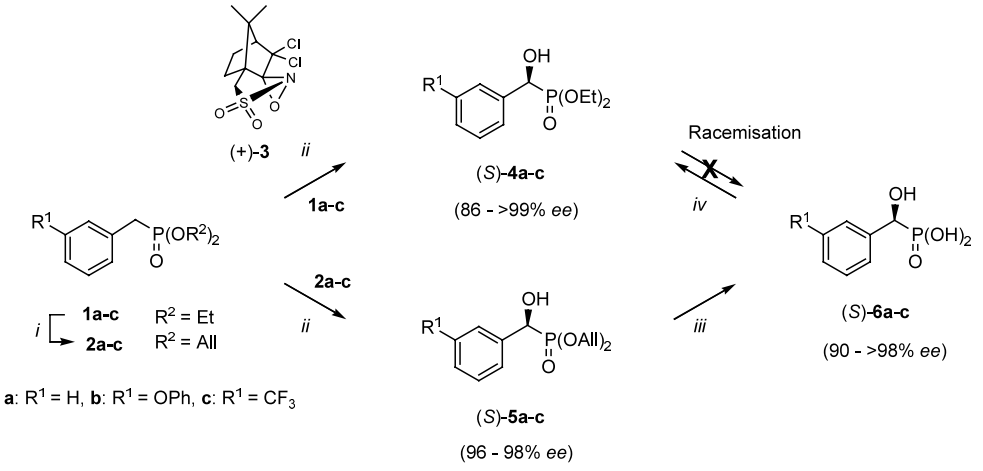
0957-4166/03/$ - see front matter
PII: S0957-4166(02)00786-3



Scheme 1. Stereoselective synthesis of α-hydroxyphosphonates and phosphonic acids via oxaziridine hydroxylation of diallyl benzylphosphonates. *Reagents and conditions*: (i) 3 equiv. TMSBr/0°C/3 h, then 3 equiv. $(COCl)_2$/cat. DMF/CH_2Cl_2/rt/1 h, then 2.1 equiv. 2-propenol/2.1 equiv. pyridine/cat. DMAP/CH_2Cl_2/−20°C to rt/18 h; (ii) 1.5 equiv. NaHMDS/THF/−78°C/20 min, then 2 equiv. (+)-(**3**)/THF/−78°C/3 h; (iii) cat. $Pd(PPh_3)_4$/10 equiv. dimedone/THF/rt/30 min; (iv) 2.1 equiv. NMe_4OH/1:1 H_2O–acetone/−5°C/30 min, dried in vacuo, then 2.1 equiv. EtBr/DME/reflux/5 h.

difluoroalkylphosphonates.[19] Herein, we report on the synthesis of chiral, non-racemic α-hydroxyphosphonates utilising the enantioselective oxaziridine-mediated hydroxylation of phosphoryl stabilised anions introduced by Wiemer et al.,[11,20] and employing key diallyl benzylphosphonates, which are readily deprotected under neutral conditions[21] to afford the corresponding phosphonic acids in high enantiomeric excess (ee).

2. Results and discussion

As part of a study into the asymmetric synthesis of sialyltransferase inhibitors, we required a series of chiral, non-racemic *meta*-substituted α-hydroxybenzylphosphonates and initially prepared the diethyl phosphonates (*S*)-**4a**–**c** (Scheme 1) and (*R*)-**4a**–**c** in high ee, employing the procedure of Pogatchnik and Wiemer.[20] It was apparent, however, that liberation of the free phosphonic acid may be accompanied by racemisation[11] and thus another phosphonate protecting group was sought. The allyl group, as a protecting group for phosphonate esters,[16] has been used extensively in our group[6,17,22] as it can be cleaved under neutral conditions and thus, the analogous diallyl phosphonates (*S*)-**5a**–**c** (Scheme 1) and (*R*)-**5a**–**c** were synthesised, expecting that deprotection of the diallyl phosphonates could be effected without racemisation.

The requisite diethyl benzylphosphonates **1a**–**c** were readily available from the corresponding benzyl halides via Arbuzov reaction[23] with triethyl phosphite. However, due to reports of low yielding Arbuzov reactions using triallyl phosphite, we prepared the desired diallyl benzylphosphonates **2a**–**c** from the diethyl benzyl phosphonates **1a**–**c** via a high-yielding, one-pot, three-step transesterification procedure (Scheme 1).[17] Low-temperature reaction of the benzyl phosphonates **1a**–**c** and **2a**–**c** with NaHMDS in THF generated the requisite phosphoryl-stabilised anions, which were then treated with (+)-8,8-(dichlorocamphor)sulfonyloxaziridine (+)-**3** as has been described,[20] to give the chiral, non-racemic α-hydroxyphosphonates (*S*)-**4a**–**c** and (*S*)-**5a**–**c**, respectively (Scheme 1), in good yields and in high ee (Table 1). The (*R*)-enantiomers were prepared in an analogous manner employing oxaziridine (−)-**3**.

The enantiomeric purity and absolute configuration of the products was established by the chemical shift differences of the ^{31}P and ^{1}H NMR spectral resonances of the (*S*)-*O*-methyl mandelate (MMA) derivatised alcohols as described by Spilling et al.[24] Employing the accepted model for the conformation of the (*S*)-*O*-MMA esters of α-hydroxyphosphonates (Scheme 2),[24] the esters derived from (*R*)-α-hydroxyphosphonates have the phosphorus atom shielded by the mandelate phenyl ring and are thus shifted upfield relative to the (*S*)-esters (e.g. entries 4 and 7, Table 1). The chemical shift differences we obtained for the phosphorus atom of the (*S*)-*O*-MMA esters of (*S*)-**4a**–**c** and (*S*)-**5a**–**c** (as well as their (*R*)-enantiomers), are in the range 0.4–0.5 ppm (Table 1), in agreement with reported values for applications of this method,[11,24] and confirmed that oxidations employing the (+)-oxaziridine reagent, (+)-**3**, afford the (*S*)-α-hydroxyphosphonates.[20]

Deprotection of the diallyl phosphonates (*S*)-**5a**–**c** and (*R*)-**5a**–**c** using $Pd(Ph_3)_4$ in the presence of dimedone as an allyl scavenger[21] gave the desired chiral, non-racemic phosphonic acids (*S*)-**6a**–**c** and (*R*)-**6a**–**c**, respectively, in high yields and showing essentially equal but opposite rotations. However, as there are no reported specific rotation values for either enantiomer of the phosphonic acids **6b** and **6c**, the ee values could not be established from the specific rotation alone. Thus, each of the (*S*)-enantiomers of phosphonic acids (*S*)-**6a**–**c** were converted to their tetramethylammonium salts, followed by S_N2 reaction with ethyl bromide in reflux-

Table 1. ^{31}P NMR shifts of the (*S*)-*O*-MMA esters of α-hydroxyphosphonates (*S*)-**4b**,**c**, (*S*)-**5a**–**c** and (*R*)-**5a**

Entry		$[\alpha]_D^{20}$	R^1	R^2	(*S*)-*O*-MMA esters		Δδ	% ee
					^{31}P NMR: δ (major)	^{31}P NMR: δ (minor)		
1	(*S*)-**4a**	−38	H	Et	–	–	–	>99[a]
2	(*S*)-**4b**	−19	OPh	Et	17.60 (93%)	17.15 (7%)	0.45	86[b]
3	(*S*)-**4c**	−27	CF_3	Et	17.06 (99%)	16.68 (1%)	0.38	98
4	(*S*)-**5a**	−29	H	All	18.80 (98%)	18.38 (2%)	0.42	96
5	(*S*)-**5b**	−16	OPh	All	18.08 (99%)	17.62 (1%)	0.46	98
6	(*S*)-**5c**	−27	CF_3	All	20.47 (98%)	20.06 (2%)	0.41	96
7	(*R*)-**5a**	+28	H	All	18.38 (98%)	18.80 (2%)	0.42	96

[a] By comparison to reported chiroptical data.
[b] Analysis of the ^{1}H NMR spectrum gives a value of 90% de.

ing DME,[25] to regenerate the diethyl phosphonates (*S*)-**4a**–**c**, in order to compare their specific rotation values to those obtained previously (Scheme 1).

The specific rotations obtained for the regenerated diethyl phosphonates (*S*)-**4a**–**c** were all somewhat lower than the previous values (cf. entries 1–3 in Table 1 with entries 1–3 in Table 2). Furthermore, conversion into their corresponding (*S*)-*O*-MMA esters and ^{1}H NMR spectroscopic analysis gave values for regenerated (*S*)-**4a**–**c** of 76, 88, and 55% ee, respectively (entries 1–3, Table 2), based on integration of the methine resonance of the mandelate component, observed upfield (0.04 to 0.07 ppm[24]) for esters derived from (*R*)-α-hydroxyphosphonates, relative to the (*S*)-esters, due to shielding by the benzyl ring. Similar ee values were obtained by ^{31}P NMR spectroscopy, as described before (entries 1–3, Table 2).

The high, essentially equal but opposite, specific rotation values of the phosphonic acid enantiomers (*S*)- and (*R*)-**6a**–**c** suggested that the loss of enantiomeric purity occurred during the esterification step[26] rather than the deprotection step. This was confirmed by conversion of the phosphonic acids (*S*)-**6a**–**c** into their corresponding methyl phosphonate esters (*S*)-**7a**–**c** via an alternative procedure employing trimethylsilyldiazomethane. In this manner, the specific rotation value obtained for (*S*)-**7a** ($[\alpha]_D^{20} = -45$ (*c* 0.8, $CHCl_3$), lit.[27] $[\alpha]_D^{20} = -46$ (*c* 1.0, acetone)) matched the reported value, showing a high degree of enantiomeric purity. There are no reported specific rotations for either enantiomer of the methyl phosphonates **7b** and **7c**, and thus the esters were further derivatised with (*S*)-*O*-MMA (Scheme 2), whereupon analysis of their ^{1}H NMR spectra revealed for (*S*)-**7a**–**c** values of 90, 94 and >98% ee, respectively (entries 4–6, Table 2), establishing that the deprotection of the allyl moiety does indeed proceed with retention of a very high degree of stereochemical integrity.

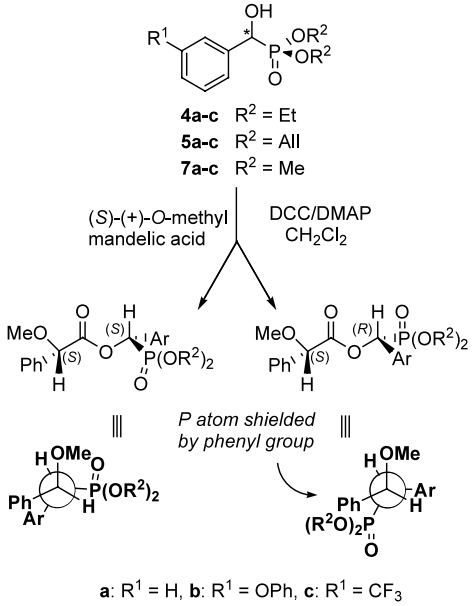
3. Conclusion

We have presented a simple and efficient stereoselective route that gives rise to both pure α-hydroxyphosphonates ((*S*)- or (*R*)-**4a**–**c**, and (*S*)- or (*R*)-**5a**–**c**) and their corresponding free phosphonic acids ((*S*)- or (*R*)-**6a**–**c**) in high ee (90 to >99% ee), via the enantioselective oxaziridine-mediated hydroxylation[11,20] of diallyl benzylphosphonates **2a**–**c**. We expect that this will be a synthetically valuable method, contributing to further investigation into the role of α-hydroxyphosphoryl compounds in biological processes.

4. Experimental

4.1. General

Unless specified otherwise, all reactions were performed under an inert atmosphere of nitrogen with dry, freshly distilled solvents under anhydrous conditions and monitored by TLC using plastic plates coated with Merck Silica Gel 60 F254 and visualised using either UV light (254 or 366 nm) or a molybdenum staining reagent.[28] All compounds were purified by flash chromatography (FC) as described by Still et al.[29] using Merck Silica Gel 60 (particle size 40–63 μm) and the yields given refer to



Scheme 2. (*S*)-*O*-Methylmandelate esters of α-hydroxyphosphonates.

Table 2. NMR Shifts of the (*S*)-*O*-MMA esters of 'regenerated' diethyl α-hydroxyphosphonates (*S*)-**4a–c** and dimethyl α-hydroxyphosphonates (*S*)-**7a–c**

Entry		$[\alpha]_D^{20}$	R^1	R^2	(*S*)-*O*-MMA esters		$\Delta\delta$	% ee
					^{1}H NMR: δ (major)	^{1}H NMR: δ (minor)		
1	(*S*)-**4a**	−36	H	Et	4.90 (88%)	4.85 (12%)	0.05	76[a]
2	(*S*)-**4b**	−18	OPh	Et	4.90 (94%)	4.83 (6%)	0.07	88[a]
3	(*S*)-**4c**	−21	CF_3	Et	4.94 (78%)	4.90 (22%)	0.04	55[a]
4	(*S*)-**7a**	−45	H	Me	4.91 (95%)	4.86 (5%)	0.05	90[b]
5	(*S*)-**7b**	−39	OPh	Me	4.89 (97%)	4.86 (3%)	0.03	94[b]
6	(*S*)-**7c**	−37	CF_3	Me	4.93 (>98%)	4.88 (<2%)	0.05	>98[b]

[a] By ^{31}P NMR spectroscopy, (*S*)-**4a**: 80% ee, (*S*)-**4b**: 90% ee, (*S*)-**4c**: 55% ee.
[b] By ^{31}P NMR spectroscopy, (*S*)-**7a**: 86% ee, (*S*)-**7b**: 94% ee, (*S*)-**7c**: >99% ee.

chromatographically and spectroscopically (^{1}H NMR) homogenous material. NMR spectra were recorded on a Bruker AC 250 Cryospec, a Bruker DRX 600, or a JEOL JNM-GX 400 instrument, where the solvent ^{1}H and ^{13}C signals, δ_H??7.24 for residual $CHCl_3$ and δ_C 77.0 for $CDCl_3$, δ_H 3.31 and δ_C 49.0 for MeOH-d_4, and δ_H 4.63 for D_2O (a drop of MeOH-d_4 was added to D_2O for referencing ^{13}C spectra), were used as internal references. For ^{31}P NMR spectra, phosphoric acid was used as an external reference. Matrix-assisted laser desorption ionisation mass spectra (MALDI-MS) were recorded on a Kratos Kompact Maldi 2, using 2,5-dihydroxybenzoic acid (DHB), hydroxycinnamic acid (CHCA) or 6-azathiothymine (ATT) as matrices. Optical rotations were measured on a Buchi polar monitor in a 1 dm cell at 22°C. Microanalyses were measured on a Heraeus CHN-O-Rapid apparatus. Reagents, including diethylbenzylphosphonate (**1a**) and both (−)- and (+)-8,8-(dichlorocamphor)sulfonyloxaziridine, (−)- or (+)-**3**, were purchased from either Fluka, Aldrich or Acros and used as supplied. *m*-Phenoxybenzylbromide was prepared and characterised as described in the literature.[30] Ee is assumed equal to the percent de calculated from integration of the ^{1}H and ^{31}P NMR spectral signals of the diastereomeric esters formed from the α-hydroxyphosphonates with (*S*)-methylmandelic acid.

4.2. Preparation of diethyl benzylphosphonates via the Michealis–Arbuzov rearrangement[23]

Triethylphosphite (1–3 equiv.) was added slowly via a dropping funnel to a two-necked round-bottomed flask fitted with a condenser and containing 1 equiv. of the neat benzylbromide. The mixture was heated to reflux and maintained at this temperature until the reaction was complete as judged by TLC, typically 1–3 h. The reflux condenser was replaced with a fractionating column and distillation head and the nascent ethyl bromide removed by distillation. The residue was purified by FC to give the desired diethyl benzylphosphonates in quantitative yield.

4.2.1. Diethyl *m*-phenoxybenzylphosphonate, 1b. From *m*-phenoxybenzylbromide[30] (15.3 g, 58.0 mmol): purification by FC (silica gel, 1:1 EtOAc–hexane, R_f=0.3) gave the desired phosphonate **1b** (18.2 g, 98% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.20 (t, ^3J=7.2 Hz, 6H, $CH_2C\underline{H}_3$), 3.07 (d, ^2J(H,P)=21.7 Hz, 2H, CH_2P), 3.98 (quin., ^3J=7.2 Hz, 4H, $C\underline{H}_2CH_3$), 6.88–7.32 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 16.3 (d, ^3J(C,P)=6.0 Hz, $CH_2\underline{C}H_3$), 33.7 (d, ^1J(C,P)=138.2 Hz), 62.1 (d, ^2J(C,P)=6.9 Hz, $\underline{C}H_2CH_3$), 117.3 (d, J(C,P)=3.8 Hz), 119.0, 120.1, 120.2, 123.3, 124.6, 124.7, 129.7, 129.8 (ArCH), 133.5 (ArC), 157.1 (ArCO), 157.4 (ArCO); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 26.7 (s, P(O)O_2); MALDI-MS (negative mode, matrix: ATT) m/z=321 ([MH]$^+$, 100%), 343 ([MNa]$^+$, 24%), 320.3 for $C_{17}H_{21}O_4P$. Calcd: C, 63.74; H, 6.61. Found: C, 63.33; H, 6.56%.

4.2.2. Diethyl *m*-trifluorobenzylphosphonate, 1c. From *m*-trifluorobenzylbromide (1.50 g, 6.30 mmol): purification by FC (silica gel, 1:1 EtOAc–hexane, R_f=0.2) gave the known phosphonate **1c** (1.81 g, 97% yield) as a colourless oil.[31] ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.25 (t, ^3J=7.2 Hz, 6H, $CH_2C\underline{H}_3$), 3.18 (d, ^2J(H,P)=21.8 Hz, 2H, CH_2P), 4.03 (quin., ^3J=7.2 Hz, 4H, $C\underline{H}_2CH_3$), 7.41–7.57 (m, 4H, ArH).

4.3. Preparation of diallyl benzylphosphonates[18]

TMSBr (3 equiv.) was added to the neat diethyl phosphonate (1 equiv.) at 0°C and the reaction stirred for 3 h, after which the excess TMSBr and the nascent ethyl bromide were removed by evaporation. The crude bis(trimethylsilyl)phosphonate was diluted with dichloromethane (10 mL), and 4 drops of DMF were added followed by the dropwise addition of oxalyl chloride (3 equiv.), resulting in the vigorous evolution of gas (CO, CO_2). The reaction mixture was stirred at rt for 1 h, after which the volatile by-products (TMSCl, CO, CO_2 and excess oxalyl chloride) were removed by rotary evaporation. The crude dichlorophosphonate was diluted with dichloromethane (5 mL), and added to a flask containing 2-propenol (2.1 equiv.), pyridine (2.1 equiv.), and 2 drops of DMAP in dichloromethane (10 mL), previously stirred together for 30 min at −10°C (salt/ice bath). The reaction mixture was stirred at −20°C for 1 h and then allowed to warm to rt and stirred overnight. The excess reactants were then removed by rotary evaporation followed by concentration under high vacuum and the residue purified by FC to give the desired diallyl phosphonates.

4.3.1. Diallyl benzylphosphonate, 2a. From **1a** (1.73 g, 7.58 mmol): purification by FC (silica gel, 8:2 CH_2Cl_2–acetone, $R_f=0.5$) gave the known phosphonate **2a** (1.37 g, 72% yield) as a colourless oil.[32] ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.18 (d, ^2J(H,P)=21.7 Hz, 2H, CH_2P), 4.38–4.46 (m, 4H, H1′), 5.18 (dq, ^3J3b′,2′)=10.4 Hz, ^2J(3b′,3a′)≈^3J(3b′,1′)=1.5 Hz, 2H, H3b′), 5.25 (dq, ^3J(3a′,2′)=17.2 Hz, ^2J(3a′,3b′)≈^3J(3a′,1′)=1.5 Hz, 2H, H3a′), 5.83 (ddt, ^3J(2′,3a′)=17.2 Hz, ^3J(2′,3b′)=10.4 Hz, ^3J(2′,1′)=5.5 Hz, 2H, H2′), 7.20–7.34 (m, 5H, ArH).

4.3.2. Diallyl *m*-phenoxybenzylphosphonate, 2b. From **1b** (3.48 g, 10.9 mmol): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.6$) gave the desired phosphonate **2b** (1.87 g, 50% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.15 (d, ^2J(H,P)=21.8 Hz, 2H, CH_2P), 4.41–4.48 (m, 4H, H1′), 5.18 (dq, ^3J(3b′,2′)=10.4 Hz, ^2J(3b′,3a′)≈^3J(3b′,1′)=1.5 Hz, 2H, H3b′), 5.27 (dq, ^3J(3a′,2′)=17.1 Hz, ^2J(3a′,3b′)≈^3J(3a′,1′)=1.5 Hz, 2H, H3a′), 5.87 (ddt, ^3J(2′,3a′)=17.1 Hz, ^3J(2′,3b′)=10.4 Hz, ^3J(2′,1′)=5.6 Hz, 2H, H2′), 6.87–7.35 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 33.8 (^1J(C,P)=137.8 Hz, CHP), 66.6 (d, ^2J(C,P)=6.0 Hz, C1′), 117.4 (d, J(C,P)=2.0 Hz), 117.9, 119.0,‡ 120.2 (d, J(C,P)=6.8 Hz), 123.4,‡ 124.5 (d, J(C,P)=6.6 Hz), 129.7, 129.8 (d, J(C,P)=3.0 Hz), 132.9 (d, J(C,P)=6.8 Hz), 133.2 (ArCH, ArC, C3′ and C2′), 157.0 (2×ArCO); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 30.5 (s, $P(O)O_2$); MALDI-MS (positive mode, matrix: DHB) $m/z=345$ ([MH]$^+$, 100%), 367 ([MNa]$^+$, 42), 344.3 for $C_{19}H_{21}O_4P$. Calcd: C, 66.27; H, 6.15. Found: C, 65.73; H, 6.13%.

4.3.3. Diallyl *m*-trifluorobenzylphosphonate, 2c. From **1c** (6.33 g, 21.4 mmol): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.6$) gave the desired phosphonate **2c** (3.29 g, 48% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.23 (d, ^2J(H,P)=21.9 Hz, 2H, CH_2P), 4.42–4.48 (m, 4H, H1′), 5.19 (dq, ^3J(3b′,2′)=10.4 Hz, ^2J(3b′,3a′)≈^3J(3b′,1′)=1.5 Hz, 2H, H3b′), 5.26 (dq, ^3J(3a′,2′)=17.2 Hz, ^2J(3a′,3b′)≈^3J(3a′,1′)=1.5 Hz, 2H, H3a′), 5.84 (ddt, ^3J(2′,3a′)=17.2 Hz, ^3J(2′,3b′)=10.4 Hz, ^3J(2′,1′)=5.3 Hz, 2H, H2′), 7.42–7.52 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 33.7 (^1J(C,P)=138.7 Hz, CH_2P), 66.5 (d, ^2J(C,P)=6.4 Hz, C1′), 118.0 (s, C3′), 123.7 (bs, ArCH), 123.9 (q, ^1J(C,F)=272.4.0 Hz, CF_3), 126.5 (bs, ArCH), 128.9 (s, C2′), 130.9 (q, ^2J(C,F)=32.0 Hz, ArC-CF_3), 132.5 (s, ArC), 132.6 (d, J(C,F)=5.8 Hz, ArCH), 133.1 (d, J(C,F)=6.1 Hz, ArCH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 29.5 (s, $P(O)O_2$); MALDI-MS (positive mode, matrix: DHB) $m/z=321$ ([MH]$^+$, 100%), 343 ([MNa]$^+$, 14), 320.1 for $C_{14}H_{16}F_3O_3P$. Calcd: C, 52.51; H, 5.04. Found: C, 52.65; H, 5.32%.

4.4. Preparation of chiral, non-racemic α-hydroxybenzylphosphonates

According to the reported procedure,[11,20] NaHMDSA (1.5 equiv.) was added dropwise to a solution of the benzylphosphonate (1 equiv.) in THF (10 mL) at −78°C and the yellow coloured solution stirred for 30 min. A solution of the oxaziridine reagent (+)- or (−)-**3** (2 equiv.) in THF (10 mL) was added dropwise via syringe and the reaction stirred for a further 3 h, while the temperature was maintained at −78°C (dry ice–acetone bath). The reaction was quenched at −78°C by the addition of saturated NH_4Cl, brought to rt, extracted several times with ethyl acetate, the combined organic fractions washed with saturated NH_4Cl, followed by saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and the residue purified by FC to give the desired α-hydroxyphosphonates.

4.4.1. Diethyl (*S*)-α-hydroxybenzylphosphonate, (*S*)-4a. From **1a** (100 mg, 0.44 mmol) and employing oxaziridine (+)-(**3**): purification by FC (silica gel, 8:2 CH_2Cl_2–acetone, $R_f=0.3$) gave the known phosphonate (*S*)-**4a** (47.9 mg, 45% yield, $[\alpha]_D^{20}=-38$ (*c* 1.3 $CHCl_3$), lit.[33] $[\alpha]_D^{20}=-38$ (*c* 2.7, $CHCl_3$), >99% ee) as a colourless oil with spectroscopic data identical to those reported.[33] *For the (S)-O-MMA ester of (S)-**4a***: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.14 (t, $J=7.1$ Hz, 3H, $CH_2C\underline{H}_3$), 1.19 (t, $J=7.1$ Hz, 3H, $CH_2C\underline{H}_3$), 3.41 (s, 3H, OMe), 3.81–4.13 (m, 4H, $C\underline{H}_2CH_3$), 4.90 (s, 1H, CH[OMe]), 6.13 (d, ^2J(H,P)=13.3 Hz, 1H, CHP), 7.12–7.42 (m, 5H, ArH).

4.4.2. Diethyl (*S*)-α-hydroxy(*m*-phenoxy)benzylphosphonate, (*S*)-4b. From **1b** (70.0 mg, 0.22 mmol) and employing oxaziridine (+)-(**3**): purification by FC (silica gel, 3:2 EtOAc–hexane, $R_f=0.3$) gave the desired phosphonate (*S*)-**4b** (18.6 mg, 25% yield, $[\alpha]_D^{20}=-19$ (*c* 1.0, $CHCl_3$)) as a colourless oil with spectroscopic data identical to those reported for its racemate.[34] *For the (S)-O-MMA ester of (S)-**4b***: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.18 (t, $J=7.1$ Hz, 3H, $CH_2C\underline{H}_3$), 1.21 (t, $J=7.1$ Hz, 3H, $CH_2C\underline{H}_3$), 3.41 (s, 3H, OMe), 3.95–4.05 (m, 4H, $C\underline{H}_2CH_3$), 4.90 (s, 1H, CH[OMe]), 6.12 (d, ^2J(H,P)=13.5 Hz, 1H, CHP), 6.83 (s, 1H, ArH), 6.91–6.92 (m, 4H, ArH), 7.10 (m, 1H, ArH), 7.16 (m, 1H, ArH), 7.26–7.32 (m, 5H, ArH), 7.38 (m, 2H, ArH), 90% ee; ^{31}P NMR ($CDCl_3$, 245 MHz): δ 17.60 (s, $P(O)O_2$, 86% ee).

4.4.3. Diethyl (*R*)-α-hydroxy(*m*-phenoxy)benzylphosphonate, (*R*)-4b. From **1b** (114 mg, 0.35 mmol) and employing oxaziridine (−)-**3**: purification by FC (silica gel, 3:2 EtOAc–hexane, $R_f=0.3$) gave the desired phosphonate (*R*)-**4b** (54.2 mg, 46% yield, $[\alpha]_D^{20}=+17$ (*c* 1.2, $CHCl_3$)) as a colourless oil with spectroscopic data identical to those of its enantiomer, (*S*)-**4b**. *For the (S)-O-MMA ester of (R)-**4b***: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.02, 1.06 (overlapping t, $J=7.1$ Hz, 6H, $CH_2C\underline{H}_3$), 3.37 (s, 3H, OMe), 3.53–3.92 (m, 4H, $C\underline{H}_2CH_3$), 4.83 (s, 1H, CH[OMe]), 6.09 (d, ^2J(H,P)=13.2 Hz, 1H, CHP), 6.90–7.48 (m, 14H, ArH).

4.4.4. Diethyl (*S*)-α-hydroxy(*m*-trifluoro)benzylphosphonate, (*S*)-4c. From **1c** (116 mg, 0.39 mmol) and employing oxaziridine (+)-(**3**): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.2$) gave the desired phosphonate (*S*)-**4c** (59.3 mg, 45% yield, $[\alpha]_D^{20}=-27$ (*c* 2.4, $CHCl_3$)) as a colourless oil, the racemate of which has

‡ Coincident peaks.

been reported.[35] ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.22 (t, $J=7.1$ Hz, 3H, $CH_2C\underline{H}_3$), 1.25 (t, $J=7.1$ Hz, 3H, $CH_2C\underline{H}_3$), 4.05 (quin., $J=7.1$ Hz, 4H, $C\underline{H}_2CH_3$), 4.33 (brs, 1H, OH), 5.08 (brd, ^2J(H,P) = 10.6 Hz, 1H, CHP), 7.40–7.78 (m, 4H, ArH). *For the (S)-O-MMA ester of (S)-**4c***: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.19, 1.21 (overlapping t, $J=7.1$ Hz, 6H, $CH_2C\underline{H}_3$), 3.43 (s, 3H, OMe), 3.97–4.07 (m, 4H, $C\underline{H}_2CH_3$), 4.94 (s, 1H, CH[OMe]), 6.16 (d, ^2J(H,P) = 13.8 Hz, 1H, CHP), 7.32–7.37 (m, 8H, ArH), 7.40 (m, 1H, ArH); ^{31}P NMR ($CDCl_3$, 245 MHz): δ 17.06 (s, $P(O)O_2$, 98% ee).

4.4.5. Diethyl (*R*)-α-hydroxy(*m*-trifluoro)benzylphosphonate, (*R*)-4c. From **1c** (131 mg, 0.44 mmol) and employing oxaziridine (−)-(**3**): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.2$) gave the desired phosphonate (*R*)-**4c** (64.4 mg, 47% yield, $[\alpha]_D^{20}=+25$ (*c* 0.4, $CHCl_3$)) as a colourless oil with spectroscopic data identical to those of its enantiomer, (*S*)-**4c**. *For the (S)-O-MMA ester of (R)-**4c***: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.07, 1.10 (overlapping t, $J=7.1$ Hz, 6H, $CH_2C\underline{H}_3$), 3.41 (s, 3H, OMe), 3.67 (m, 1H, Ha of $C\underline{H}_2CH_3$), 3.85 (m, 2H, $C\underline{H}_2CH_3$), 3.92 (m, 1H, Hb of $C\underline{H}_2CH_3$), 4.90 (s, 1H, CH[OMe]), 6.17 (d, ^2J(H,P) = 13.6 Hz, 1H, CHP), 7.35–7.39 (m, 3H, ArH), 7.45–7.51 (m, 3H, ArH), 7.51 (m, 1H, ArH), 7.63 (m, 1H, ArH), 7.68 (m, 1H, ArH); ^{31}P NMR ($CDCl_3$, 245 MHz): δ 16.68 (s, $P(O)O_2$, 98% ee).

4.4.6. Diallyl (*S*)-α-hydroxybenzylphosphonate, (*S*)-5a. From **2a** (613 mg, 2.43 mmol) and employing oxaziridine (+)-(**3**): purification by FC (silica gel, 8:2 CH_2Cl_2–acetone, $R_f=0.4$) gave the desired phosphonate (*S*)-**5a** (236 mg, 36% yield, $[\alpha]_D^{20}=-29$ (*c* 1.0, $CHCl_3$)) as a colourless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.31–4.54 (m, 5H, H1′ and OH), 5.04 (dd, J(H,OH) = 4.9, ^2J(H,P) = 10.9 Hz, 1H, CHP), 5.12–5.30 (m, 4H, H3′), 5.73–5.93 (m, 2H, H2′), 7.27–7.37 (m, 3H, *m*- and *p*-ArH), 7.43–7.50 (m, 2H, *o*-ArH); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 67.3 (d, ^2J(C,P) = 7.0 Hz, C1′), 67.6 (d, ^2J(C,P) = 6.9 Hz, C1′), 70.8 (^1J(C,P) = 159.5 Hz, CHP), 117.9 (d, ^4J(C,P) = 3.2 Hz, C3′), 127.2‡ (d, J(C,P) = 5.9 Hz, ArCH), 128.0 (d, J(C,P) = 3.5 Hz, ArCH), 128.1‡ (d, J(C,P) = 2.1 Hz, ArCH), 132.7 (d, ^3J(C,P) = 5.9 Hz, C2′), 136.5 (d, ^2J(C,P) = 2.0 Hz, ArC); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 26.2 (s, $P(O)O_2$); MALDI-MS (positive mode, matrix: DHB) $m/z=269$ ($[MH]^+$, 100%), 273 ($[M-H_2O+Na]^+$, 30), 279 (26), 291 ($[MNa]^+$, 24), 268.2 for $C_{13}H_{17}O_4P$. Calcd: C, 58.21; H, 6.39. Found: C, 58.06; H, 6.23%. *For the (S)-O-MMA ester of (S)-5a*: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.42 (s, 3H, OMe), 4.36 (m, 2H, H1′), 4.44 (m, 2H, H1′), 4.91 (s, 1H, CH[OMe]), 5.15–5.27 (m, 4H, H3′), 5.78 (m, 2H, H2′), 6.18 (d, ^2J(H,P) = 13.3 Hz, 1H, CHP), 7.14–7.20 (m, 5H, ArH), 7.32–7.33 (m, 3H, *m*- and *p*-ArH), 7.39–7.40 (m, 2H, *o*-ArH); ^{31}P NMR ($CDCl_3$, 245 MHz): δ 18.80 (s, $P(O)O_2$, 96% ee).

4.4.7. Diallyl (*R*)-α-hydroxybenzylphosphonate, (*R*)-5a. From **2a** (748 mg, 3.00 mmol) and employing oxaziridine (−)-(**3**): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.4$) gave the desired phosphonate (*R*)-**5a** (380 mg, 48% yield, $[\alpha]_D^{20}=+28$ (*c* 0.7, $CHCl_3$)) as a colourless oil with spectroscopic data identical to those of its enantiomer, (*S*)-**5a**. *For the (S)-O-MMA ester of (R)-**5a***: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.40 (s, 3H, OMe), 3.98 (m, 1H, Ha-1′), 4.20 (m, 1H, Hb-1′), 4.25–4.30 (m, 2H, H1′), 4.88 (s, 1H, CH[OMe]), 5.09–5.16 (m, 4H, H3′), 5.63–5.66 (m, 2H, H2′), 6.18 (d, ^2J(H,P) = 13.1 Hz, 1H, CHP), 7.34–7.37 (m, 6H, ArH), 7.47–7.50 (m, 4H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 18.38 (s, $P(O)O_2$, 96% ee).

4.4.8. Diallyl (*S*)-α-hydroxy(*m*-phenoxy)benzylphosphonate, (*S*)-5b. From **2b** (1.16 mg, 3.37 mmol) and employing oxaziridine (+)-(**3**): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.4$) gave the desired phosphonate (*S*)-**5b** (559 mg, 46% yield, $[\alpha]_D^{20}=-16$ (*c* 0.9, $CHCl_3$)) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.33–4.58 (m, 5H, H1′ and OH), 5.01 (d, ^2J(H,P) = 10.6 Hz, 1H, CHP), 5.15–5.33 (m, 4H, H3′), 5.73–5.95 (m, 2H, H2′), 6.90–7.36 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 67.3 (d, ^2J(C,P) = 7.2 Hz, C1′), 67.7 (d, ^2J(C,P) = 6.9 Hz, C1′), 70.7 (^1J(C,P) = 158.9 Hz, CHP), 117.7 (d, J(C,P) = 8.9 Hz, ArCH), 118.1 (d, ^4J(C,P) = 4.7 Hz, C3′), 118.5 (d, J(C,P) = 3.6 Hz), 118.9, 122.0 (d, J(C,P) = 5.8 Hz), 123.3,‡ 129.5 (d, J(C,P) = 2.3 Hz), 129.7,‡ 132.6 (d, J(C,P) = 5.8 Hz, ArCH and C2′), 138.5 (ArC), 157.1 (ArCO), 157.2 (ArCO); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 22.4 (s, $P(O)O_2$); MALDI-MS (positive mode, matrix: DHB) $m/z=361$ ($[MH]^+$, 100%), 383 ($[MNa]^+$, 72), 360.3 for $C_{19}H_{21}O_5P$. Calcd: C, 63.33; H, 5.87. Found: C, 62.81; H, 5.83%. *For the (S)-O-MMA ester of (S)-**5b***: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.38 (s, 3H, OMe), 4.28–4.50 (m, 4H, H1′), 4.87 (s, 1H, CH[OMe]), 5.10–5.28 (m, 4H, H3′), 5.67–5.85 (m, 2H, H2′), 6.12 (d, ^2J(H,P) = 13.5 Hz, 1H, CHP), 6.78–7.39 (m, 14H, ArH); ^{31}P NMR ($CDCl_3$, 245 MHz): δ 18.08 (s, $P(O)O_2$, 98% ee).

4.4.9. Diallyl (*R*)-α-hydroxy(*m*-phenoxy)benzylphosphonate, (*R*)-5b. From **2b** (764 mg, 2.22 mmol) and employing oxaziridine (−)-(**3**): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.4$) gave the desired phosphonate (*R*)-**5b** (338 mg, 42% yield, $[\alpha]_D^{20}=+17$ (*c* 1.3, $CHCl_3$)) as a pale yellow oil with spectroscopic data identical to those of its enantiomer, (*S*)-**5b**. *For the (S)-O-MMA ester of (R)-**5b***: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.36 (s, 3H, OMe), 3.92–4.35 (m, 4H, H1′), 4.82 (s, 1H, CH[OMe]), 5.05–5.18 (m, 4H, H3′), 5.54–5.70 (m, 2H, H2′), 6.13 (d, ^2J(H,P) = 13.8 Hz, 1H, CHP), 6.88–7.45 (m, 14H, ArH); ^{31}P NMR ($CDCl_3$, 245 MHz): δ 17.62 (s, $P(O)O_2$, 98% ee).

4.4.10. Diallyl (*S*)-α-hydroxy(*m*-trifluoro)benzylphosphonate, (*S*)-5c. From **2c** (799 mg, 2.49 mmol) and employing oxaziridine (+)-(**3**): purification by FC (silica gel, 7:3 CH_2Cl_2–acetone, $R_f=0.6$) gave the desired phosphonate (*S*)-**5c** (349 mg, 42% yield, $[\alpha]_D^{20}=-27$ (*c* 2.8, $CHCl_3$)) as a colourless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.44–4.53 (m, 4H, H1′), 5.10 (dd, J(H,OH) = 5.7, ^2J(H,P) = 11.3 Hz, 1H, CHP), 5.16–5.33 (m, 5H, H3′ and OH), 5.72–5.92 (m, 2H, H2′), 7.40–7.78 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 67.4 (d, ^2J(C,P) = 7.2 Hz, C1′), 67.9 (d, ^2J(C,P) = 6.9 Hz, C1′),

70.3 (^1J(C,P) = 159.6 Hz, CHP), 118.4 (s, C3′), 124.0 (bs, ArCH), 130.7 (q, ^1J(C,F) = 258.6 Hz, CF_3), 124.8 (bs, ArCH), 128.6 (s, C2′), 130.3 (d, J(C,F) = 5.2 Hz, ArCH), 130.7 (q, ^2J(C,F) = 29.2 Hz, ArC-CF_3), 132.5 (d, J(C,F) = 5.8 Hz, ArCH), 137.7 (s, ArC); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 24.84 (s, $P(O)O_2$); MALDI-MS (positive mode, matrix: DHB) m/z = 337 ($[MH]^+$, 100%), 359 ($[MNa]^+$, 74), 336.1 for $C_{14}H_{16}F_3O_4P$. Calcd: C, 50.01; H, 4.80. Found: C, 50.32; H, 5.50%. *For the (S)-O-MMA ester of (S)-**5c***: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.39 (s, 3H, OMe), 4.32–4.52 (m, 4H, H1′), 4.91 (s, 1H, CH[OMe]), 5.15–5.27 (m, 4H, H3′), 5.68–5.83 (m, 2H, H2′), 6.19 (d, ^2J(H,P) = 13.9 Hz, 1H, CHP), 7.28–7.51 (m, 9H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 20.47 (s, $P(O)O_2$, 96% ee).

4.4.11. Diallyl (*R*)-α-hydroxy(*m*-trifluoro)benzylphosphonate, (*R*)-5c. From **2c** (907 mg, 2.83 mmol) and employing oxaziridine (–)-(**3**): purification by FC (silica gel, 7:3 CH_2Cl_2–acetone, R_f = 0.6) gave the desired phosphonate (*R*)-**5c** (453 mg, 45% yield, $[\alpha]_D^{20}$ = +25 (*c* 2.7, $CHCl_3$)) as a colourless oil with spectroscopic data identical to those of its enantiomer, (*S*)-**5c**. *For the (S)-O-MMA ester of (R)-**5c***: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.38 (s, 3H, OMe), 3.95–4.48 (m, 4H, H1′), 4.88 (s, 1H, CH[OMe]), 5.07–5.20 (m, 4H, H3′), 5.56–5.73 (m, 2H, H2′), 6.18 (d, ^2J(H,P) = 13.8 Hz, 1H, CHP), 7.37–7.70 (m, 9H, ArH); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 20.06 (s, $P(O)O_2$, 96% ee).

4.5. Deprotection of the diallyl α-hydroxybenzylphosphonates

To a solution of the diallyl α-hydroxyphosphonates (1 equiv.) in THF (10 mL) at rt, dimedone (10 equiv.) was added, the flask covered with foil and $Pd(PPh_3)_4$ (0.2 equiv.) added. The reaction was stirred at rt for 30 min, concentrated and purified by RP FC to give the free phosphonic acids.

4.5.1. (*S*)-α-Hydroxybenzylphosphonic acid, (*S*)-6a. From (*S*)-**5a** (50.0 mg, 0.19 mmol): purification by RP FC (C_{18} silica gel, 1:3 EtOH–H_2O, R_f = 0.9) gave the known phosphonic acid (*S*)-**6a** (35.7 mg, 100% yield) as a colourless amorphous solid, with spectroscopic data identical to those reported for its racemate.[36] For further characterisation and storage, the remaining phosphonic acid (*S*)-**6a** not employed in subsequent reactions was subjected to ion exchange (IR 120 Na+), followed by precipitation from EtOH and lyophilisation from water, which gave the known disodium salt of (*S*)-**6a** ($[\alpha]_D^{20}$ = –23 (*c* 0.4, 3:1 MeOH–H_2O).[37]

4.5.2. (*R*)-α-Hydroxybenzylphosphonic acid, (*R*)-6a. From (*R*)-**5a** (47.5 mg, 0.18 mmol): purification by RP FC (C_{18} silica gel, 1:3 EtOH–H_2O, R_f = 0.9) gave the desired phosphonic acid (*R*)-**6a** (33.9 mg, quantitative yield) as a colourless amorphous solid with spectroscopic data identical to those of its enantiomer, (*S*)-**6a**. For further characterisation and storage, the phosphonic acid (*R*)-**6a** was subjected to ion exchange (IR 120 Na+), followed by precipitation from EtOH and lyophilisation from water, which gave the known disodium salt of (*R*)-**6a** (21.9 mg, 52% yield, $[\alpha]_D^{20}$ = +21 (*c* 0.4, 3:1 MeOH–H_2O)), lit.[37] $[\alpha]_D^{20}$ = +27 (*c* 0.2, H_2O)).

4.5.3. (*S*)-α-Hydroxy(*m*-phenoxy)benzylphosphonic acid, (*S*)-6b. From (*S*)-**5b** (38.1 mg, 0.11 mmol):[§] purification by RP FC (C_{18} silica gel, 1:3 EtOH–H_2O, R_f = 0.3) gave the known phosphonic acid[38] (*S*)-**6a** (15.1 mg, 51% yield) as a colourless amorphous solid, ^{1}H NMR (D_2O, 250 MHz): δ 4.53 (d, ^2J(H,P) = 12.9 Hz, 1H, CHP), 6.52–7.18 (m, 9H, ArH). For further characterisation and storage, the remaining phosphonic acid (*S*)-**6a** not employed in subsequent reactions was subjected to ion exchange (IR 120 Na+), followed by precipitation from EtOH and lyophilisation from water, which gave the desired sodium salt of (*S*)-**6b** ($[\alpha]_D^{20}$ = –22 (*c* 0.2, H_2O)). *Sodium salt of (S)-**6b***: ^{1}H NMR (D_2O, 250 MHz): δ 4.47 (d, ^2J(H,P) = 12.2 Hz, 1H, CHP), 6.69–7.28 (m, 9H, ArH); ^{13}C NMR (D_2O, 63 MHz): δ 72.8 (d, ^1J(C,P) = 152.3 Hz, CHP), 118.4, 118.6, 119.9,[‡] 123.4, 124.8, 130.7, 131.0[‡] (ArCH), 142.7, 157.5, 157.7 (ArC); ^{31}P NMR ($CDCl_3$, 245 MHz): δ 19.8 (s, $P(O)O_2$, 98% ee). MALDI-MS (positive mode, matrix: DHB) m/z = 347 ($[MNa]^+$, 100%), 324.2 for $C_{13}H_{11}Na_2O_5P$.

4.5.4. (*R*)-α-Hydroxy(*m*-phenoxy)benzylphosphonic acid, (*R*)-6b. From (*R*)-**5b** (174 mg, 0.48 mmol): purification by RP FC (C_{18} silica gel, 1:3 EtOH–H_2O, R_f = 0.3) gave the desired phosphonic acid (*R*)-**6b** (135 mg, quantitative yield) as a colourless amorphous solid with spectroscopic data identical to those of its enantiomer, (*S*)-**6b**. For further characterisation and storage, the phosphonic acid (*R*)-**6b** was subjected to ion exchange (IR 120 Na+), followed by precipitation from EtOH and lyophilisation from water, which gave the desired sodium salt of (*R*)-**6b** (15.1 mg, 32% yield, $[\alpha]_D^{20}$ = +20 (*c* 0.1, 50% aq. DMSO)), as a colourless lyophilisate with spectroscopic data identical to those of its enantiomer, (*S*)-**6b**.

4.5.5. (*S*)-α-Hydroxy(*m*-trifluoro)benzylphosphonic acid, (*S*)-6c. From (*S*)-**5c** (142 mg, 0.43 mmol): purification by RP FC (C_{18} silica gel, 1:3 EtOH–H_2O, R_f = 0.4) gave the desired phosphonic acid (*S*)-**6c** (70.3 mg, 65% yield) as a colourless amorphous solid, ^{1}H NMR (D_2O, 250 MHz): δ 4.78 (d, ^2J(H,P) = 12.0 Hz, 1H, CHP), 7.47 (m, 2H, ArH), 7.72–7.88 (m, 2H, ArH). For further characterisation and storage, the remaining phosphonic acid (*S*)-**6c** not employed in subsequent reactions was subjected to ion exchange (IR 120 Na+), followed by precipitation from EtOH and lyophilisation from water, which gave the desired sodium salt of (*S*)-**6c** ($[\alpha]_D^{20}$ = –16 (*c* 1.1, 1:3 acetone–H_2O)). *Sodium salt of (S)-**6c***: ^{1}H NMR (D_2O, 250 MHz): δ 4.70 (d, ^2J(H,P) = 12.7 Hz, 1H, CHP), 7.30–7.64 (m, 4H, ArH); ^{13}C NMR (D_2O, 245 MHz): δ 73.1 (d, ^1J(C,P) = 148.4 Hz, CHP), 124.6 (ArCH), 124.8 (ArCH), 125.3 (q, ^1J(C,P) = 271.8 Hz, CF_3), 129.6 (ArCH), 130.7 (q, ^2J(C,P) = 33.2 Hz, ArC-CF_3), 131.6 (ArCH), 142.0 (ArC); ^{31}P NMR ($CDCl_3$, 245 MHz): δ 16.4 (s, $P(O)O_2$). MALDI-MS (positive

[§] Dimedone was replaced with diisopropylamine to assist purification.

mode, matrix: DHB) $m/z=301$ ($[MH]^+$, 64%), 279 ($[M-Na+2H]^+$, 36%); MALDI-MS (negative mode, matrix: ATT) $m/z=255$ ($[M-2Na+H]^-$, 100%), 300.1 for $C_8H_6F_3Na_2O_4P$.

4.5.6. (*R*)-α-Hydroxy(*m*-trifluoro)benzylphosphonic acid, (*R*)-6c. From (*R*)-**5c** (89.8 mg, 0.27 mmol): purification by RP FC (C_{18} silica gel, 1:3 EtOH–H_2O, $R_f=0.4$) gave the desired phosphonic acid (*R*)-**6c** (37.5 mg, 55% yield) as a white amorphous solid with spectroscopic data identical to those of its enantiomer, (*S*)-**6c**. For further characterisation and storage, the phosphonic acid (*R*)-**6c** was subjected to ion exchange (IR 120 Na+), followed by precipitation from EtOH and lyophilisation from water, which gave the desired sodium salt of (*R*)-**5c** ($[\alpha]_D^{20}=+15$ (*c* 1.2, 1:3 acetone–H_2O)), as a colourless lyophilisate with spectroscopic data identical to those of its enantiomer, (*S*)-**6c**.

4.6. Regeneration of the diethyl phosphonates

To a freshly prepared solution of the free phosphonic acid in of 1:1 acetone–H_2O (2 mL), a 5% aq. solution of tetramethylammonium hydroxide (2 equiv.) was added dropwise, while the reaction mixture was maintained at −5 to −10°C (salt/ice-bath). The reaction mixture was stirred for 30 min and thereafter, the solvent removed by rotary evaporation at <40°C and the residue dried in vacuo overnight. Ethyl bromide (2 equiv.) was then added to a solution of the tetramethylammonium salts in DME (5 mL) and the mixture refluxed for 5 h, cooled, filtered, the filtrate concentrated and the residue purified by FC to give the desired diethyl phosphonates.

4.6.1. Diethyl (−)-(*S*)-α-hydroxybenzylphosphonate, (*S*)-4a. From (*S*)-**6a** (21.8 mg, 0.12 mmol): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.3$) gave phosphonate (*S*)-**4a** (13.1 mg, 46% yield, $[\alpha]_D^{20}=-36$ (*c* 0.5, $CHCl_3$)), as a colourless oil. Esterification of (*S*)-**4a** with (*S*)-*O*-MMA and analysis as described previously revealed: ^{31}P NMR (163 MHz): 80% ee, ^{1}H NMR (250 MHz): 76% ee.

4.6.2. Diethyl (*S*)-α-hydroxy(*m*-phenoxy)benzylphosphonate, (*S*)-4b. From (*S*)-**6b** (54.1 mg, 0.19 mmol): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.3$) gave phosphonate (*S*)-**4b** (26.4 mg, 45% yield, $[\alpha]_D^{20}=-18$ (*c* 1.1, $CHCl_3$)), as a colourless oil. Esterification of (*S*)-**4b** with (*S*)-*O*-MMA and analysis as described previously revealed: ^{31}P NMR (245 MHz): 90% ee, ^{1}H NMR (250 MHz): 88% ee.

4.6.3. Diethyl (*S*)-α-hydroxy(*m*-trifluoro)benzylphosphonate, (*S*)-4c. From (*S*)-**6c** (40.1 mg, 0.16 mmol): purification by FC (silica gel, 3:2 EtOAc–hexane, $R_f=0.3$) gave phosphonate (*S*)-**4c** (15.0 mg, 30% yield, $[\alpha]_D^{20}=-21$ (*c* 0.5, $CHCl_3$)), as a colourless oil. Esterification of (*S*)-**4c** with (*S*)-*O*-MMA and analysis as described previously revealed: ^{31}P NMR (163 MHz): 55% ee, ^{1}H NMR (250 MHz): 55% ee.

4.7. Determination of the ee of deprotection products through preparation of dimethyl phosphonates

To a solution of the phosphonic acids (1 equiv.) in MeOH–benzene (1:3, 4 mL), $TMSCHN_2$ (2.6 equiv.) was added and the reaction mixture stirred at rt for 30 min, then concentrated under reduced pressure and the residue purified by FC to give the desired dimethyl phosphonates in good yield.

4.7.1. Dimethyl (*S*)-α-hydroxybenzylphosphonate, (*S*)-7a. From (*S*)-**6a** (30.2 mg, 0.16 mmol): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.3$) gave the known phosphonate (*S*)-**7a** (20.1 mg, 58% yield, $[\alpha]_D^{20}=-45$ (*c* 0.8, $CHCl_3$), lit.[27] $[\alpha]_D^{20}=-46$ (*c* 1.0, acetone)), as colourless crystalline material, with spectroscopic data identical to those reported. *For the (S)-O-MMA ester of (S)-7a*: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.40 (s, 3H, OMe), 3.58 (d, $^3J(H,P)=10.6$ Hz, 3H, OMe), 3.60 (d, $^3J(H,P)=10.7$ Hz, 3H, OMe), 4.91 (s, 1H, CH[OMe]), 6.16 (d, $^2J(H,P)=13.3$ Hz, 1H, CHP), 7.10–7.44 (m, 10H, ArH), 90% ee. ^{31}P NMR ($CDCl_3$, 245 MHz): δ 18.00 (s, $P(O)O_2$, 86% ee).

4.7.2. Dimethyl (*S*)-α-hydroxy(*m*-phenoxy)benzylphosphonate, (*S*)-7b. From (*S*)-**6b** (46.5 mg, 0.17 mmol): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.3$) gave the phosphonate (*S*)-**7b** (29.2 mg, 57% yield, $[\alpha]_D^{20}=-39$ (*c* 0.9, $CHCl_3$)), as colourless crystalline material with spectroscopic data identical to those reported for its racemate.[34] *For the (S)-O-MMA ester of (S)-7b*: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.39 (s, 3H, OMe), 3.51 (d, $^3J(H,P)=10.7$ Hz, 3H, OMe), 3.62 (d, $^3J(H,P)=10.7$ Hz, 3H, OMe), 4.89 (s, 1H, CH[OMe]), 6.13 (d, $^2J(H,P)=13.3$ Hz, 1H, CHP), 6.78–7.40 (m, 14H, ArH), 94% ee. ^{31}P NMR ($CDCl_3$, 245 MHz): δ 17.57 (s, $P(O)O_2$, 94% ee).

4.7.3. Dimethyl (*S*)-α-hydroxy(*m*-trifluoro)benzylphosphonate, (*S*)-7c. From (*S*)-**6c** (20.7 mg, 80.8 μmol): purification by FC (silica gel, 3:1 EtOAc–hexane, $R_f=0.3$) gave phosphonate (*S*)-**7c** (11.4 mg, 57% yield, $[\alpha]_D^{20}=-37$ (*c* 0.6, $CHCl_3$)), as colourless crystalline material. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.72 (d, $^2J(H,P)=10.1$ Hz, 6H, OMe), 4.20 (m, 1H, OH), 5.12 (d, $^2J(H,P)=11.9$ Hz, 1H, CHP), 7.45–7.79 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 53.8 ($^2J(C,P)=7.4$ Hz, OMe), 54.1 ($^2J(C,P)=6.9$ Hz, OMe), 70.2 ($^1J(C,P)=59.0$ Hz, CHP), 123.7, 125.0, 128.9 (d, $J(C,F)=2.0$ Hz), 130.3 (ArCH), 137.4 (ArC), ArC-CF_3 and CF_3 not detected; MALDI-MS (positive mode, matrix: CHCA) $m/z=285$ ($[MH]^+$, 30%), 307 ($[MNa]^+$, 100), 284.2 for $C_{10}H_{12}F_3O_4P$. *For the (S)-O-MMA ester of (S)-7c*: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.41 (s, 3H, OMe), 3.63 (d, $^3J(H,P)=10.8$ Hz, 3H, OMe), 3.64 (d, $^3J(H,P)=10.7$ Hz, 3H, OMe), 4.93 (s, 1H, CH[OMe]), 6.19 (d, $^2J(H,P)=13.8$ Hz, 1H, CHP), 7.34 (m, 4H, ArH), >98% ee. ^{31}P NMR ($CDCl_3$, 245 MHz): δ 17.10 (s, $P(O)O_2$, >99% ee).

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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