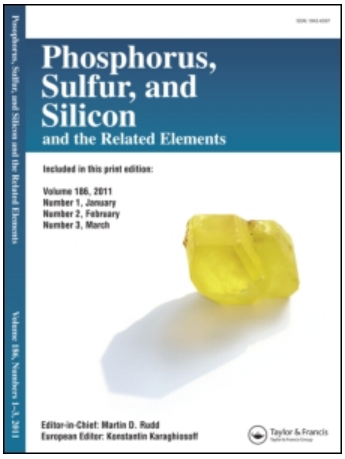

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STEREOSELECTIVE SYNTHESIS AND CRYSTAL STRUCTURE OF ( )-1*S*-BENZYL-1-(DIPHENYLPHOSPHINYL) PROPANOIC ACID

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STEREOSELECTIVE SYNTHESIS AND CRYSTAL STRUCTURE OF (+)-1*S*-BENZYL-1-(DIPHENYLPHOSPHINYL) PROPANOIC ACID

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Lithiation of (-)-menthyl 1-(diphenylphosphinyl)propanoate and subsequent alkylation with benzyl bromide gives, after ester cleavage, the title compound in 70% yield and >95% enantiomeric excess. Single crystal x-ray analysis shows this, the first reported example of an optically pure α-phosphinylcarboxylic acid, to be the *S* isomer. Molecules in the crystal are linked by strong, near-linear hydrogen bonds between the carboxylate hydrogen and phosphinyl oxygen resulting in an infinite one-dimensional chain.

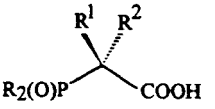
Keywords: 1-S-Benzyl-1-(diphenylphosphinyl)propanoic acid; stereoselective synthesis; X-ray crystal structure

INTRODUCTION

Chiral complexes of metal ions in high oxidation states such as Ti(IV) and Mo(VI) show promise as enantioselective oxidation catalysts for converting prochiral sulfides to sulfoxides. We have used a range of homochiral phosphorylalcoholate ligands in such systems.[1] The hard-donor oxygen atoms and bidentate character of the ligands confer high stability on the complexes formed. α-Phosphinyl carboxylates derived from compounds of type **I** promise to be even more versatile in their ligand properties, but our exhaustive attempts to synthesise and isolate the enantiomers of 1-(diphenylphosphinyl)propanoic acid proved fruitless as the compound is

* Corresponding Author.

inherently prone to racemisation under a range of conditions, due largely to the labile α-proton.[2]



I

Replacement of this hydrogen with a non-labile group should block this racemisation process, and we report here a method for the stereoselective synthesis of one such example, (+)-1*S*-benzyl-1-(diphenylphosphinyl)propanoic acid, in good yield and high enantiometric excess. This method is likely to be applicable to other derivatives.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AM 200 spectrometer operating in the Fourier transform mode. 1-(Diphenylphosphinyl)propanoic acid and (-)-menthyl 1-(diphenylphosphinyl)propanoate were prepared as previously described.[2] The menthyl ester was obtained as a 1:1 mixture of diastereoisomers.

(-)-Menthyl 1-benzyl-1-(diphenylphosphinyl)propanoate

To a stirred solution of (-)-menthyl 1-(diphenylphosphinyl)propanoate racemic ester (5 g, 12.2 mmol) in dry thf (50 ml) under a nitrogen atmosphere was added a solution of lithium diisopropylamide (2M in thf, 10% excess). After 15 mins, a solution of benzyl bromide (10% excess) in thf (50 ml) was added and the mixture was refluxed for 18 hours. The precipitated LiBr was removed by filtration and the filtrate concentrated *in vacuo*. The residue was partitioned between water (300 ml) and Et_2O (500 ml). The organic phase was washed with 5% aq. HCl, H_2O, saturated $NaHCO_3$ and then H_2O again. After drying over anhydrous Na_2SO_4 the solvent was removed to leave a pale brown oil (yield 95%), shown by ^{31}P NMR spectroscopy to be > 4:1 *S*:*R* diasteriomeric ratio. (The diasteriomer with *S* configuration at the α-carbon has a chemical shift of +34.7 ppm, whereas the *R* form has $\delta = +33.9$). The residue was chromatographed (dry column,

4 × 10 cm SiO_2, 0.5 to 5.0% thf in CH_2Cl_2 with 0.5% increments between fractions) to give the product with the *S* (propanoate) isomer in > 12:1 diasteriomeric excess (yield 76%). ^1H NMR in $CDCl_3$: *S*(propanoate) isomer; 7.0 – 8.3 (15H, aromatics), 4.43dt (1H), 3.46dd (1H), 3.12dd (1H), 1.32d (3H), 0.77d (3H), 0.67d (3H), 0.53d (3H), other menthyl protons not assigned: *R* (propanoate) isomer; 7.0 – 8.5 (15H, aromatics), 4.44dt (1H), 3.51dd (1H), 2.88dd (1H), 1.31d (3H), 0.78d (3H), 0.67d (3H), 0.54d (3H), other menthyl protons not assigned. ^{31}P NMR ($CDCl_3$) : *S* (propanoate) isomer; 34.7 ppm; *R*(propanoate) isomer, 33.9ppm.

(+)-1S-Benzyl-1S-(diphenylphosphinyl)propanoic acid

To a stirred solution of the *S*-enriched ester (1g) from above in dry CH_2Cl_2 (20 ml) at 0° under a nitrogen atmosphere was added a solution of BBr_3 (1M, 20 ml in CH_2Cl_2). The mixture was stirred at 0° for 1hr, then left for 3 days, after which it was carefully hydrolysed by dropwise addition of H_2O (40 ml) at 0° under nitrogen. The organic phase was dried over $MgSO_4$ (anhydr.) and the solvent removed *in vacuo* to leave a brown solid. This was boiled in toluene to remove the colouration, filtered, washed with acetone and then acetonitrile, and air dried. Crystallisation from 1:1 MeOH/$CHCl_3$ at 4° gave the product as colourless crystals suitable for x-ray analysis (yield 0.7g, 80%). Found: C, 72.1; H, 5.7%: Required for $C_{22}H_{21}O_3P$: C, 72.50; H, 5.82%. $[\alpha]_D = +13.6°$ (1.42% in 1:1 MeOH/CH_2Cl_2 containing 1% diisopropylamine). ^1H NMR ($CDCl_3/CD_3OD$); 7.79m (2H), 7.63d (2H), 7.29m (6H), 6.93m (5H), 3.30dd (1H), 2.73dd (1H), 1.02d (3H). ^{31}P NMR ($CDCl_3/CD_3OD$); 36.8 ppm.

Crystallography

Details of data collection procedures and structure refinement are given in Table 1. Crystals of the title complex were obtained as colourless prisms. A single crystal of suitable size was attached to a glass fibre using acrylic resin, and mounted on a goniometer head in a general position. Data were collected on an Enraf-Nonius Turbo CAD4 diffractometer, running under CAD4-Express software, and using graphite monochromated X-radiation (λ=0.71073 Å). An ω-2θ scan-mode was used. Unit cell dimensions were determined by refinement of the setting angles of 25 reflections. Standard reflections were measured every 2h during data collection, and no significant variations were noted. Lorentz-polarization corrections were then

applied to the reflection data. The structure was solved by direct methods (SIR92).[3] All non-H atoms were allowed anisotropic thermal motion. Hydrogen atoms were included at calculated positions, with C-H = 0.96 Å, except for H(1) which was freely refined. Refinement (SHELXL93)[4] was by full-matrix least-squares on F^2, using the weighting scheme $w = [\sigma^2(F_o)^2 + (0.0465P)^2 + 0.5431P]^{-1}$ where $P = [F_o^2/3 + 2F_c^2/3]$. $\sigma(F_o)^2$ was estimated from counting statistics. The neutral atom scattering factors embedded in the program SHELXL93[4] were used, with corrections applied for anomalous dispersion. Thermal elipsoidal plots were drawn with the program Ortep-3 for Windows.[5]

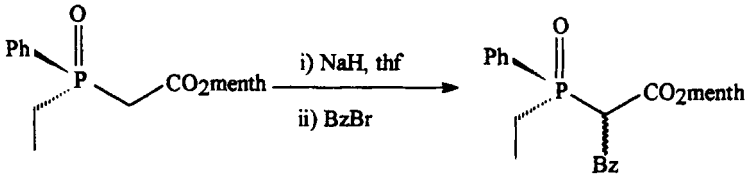
TABLE I Experimental details of the crystallographic study

Compound formula	$C_{22}H_{21}O_3P$
Formula weight	364.36
Temperature	292(2) K
Wavelength	0.71073Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions/Å	a, 9.3815(6); b, 11.5662(8); c, 17.365(2)
Volume	1884.2(3)Å^3
Z	4
Density (calculated)	1.284 g.cm^{-3}
Absorption coefficient	0.164 mm^{-1}
F(000)	786
Crystal size	0.50 × 0.40 × 0.30 mm
θ Range	2.35 to 24.98°
Index ranges	$-1 \le h \le 11, -1 \le k \le 13, -20 \le l \le 2$
Reflections collected	2599
Independent reflections	2395 [R(int) = 0.0295]
Absorption correction	None
Refinement method	Full matrix least squares on F^2
Data / restraints / parameters	2395 / 0 / 242
Goodness-of-fit on F^2	1.088
Final R indices [I>2σ (I)]	R1 = 0.0334, ωR2 = 0.0875
R indices (all data)	r1 = 0.0350, ωR2 = 0.0901
Absolute structure parameter	0.01(12)
Extinction coefficient	0.0029(8)
Largest diff. peak and hole	0.270 and −0.176 e.Å^{-3}

Complete atomic coordinates, thermal parameters and bond lengths and angles are deposited at the Cambridge Crystallographic Data Centre.

RESULTS AND DISCUSSION

Diastereoselective alkylation of chiral enolates is a well established area in asymmetric synthesis,[6] and many general examples are listed in the literature. Details of diastereoselective alkylations at a carbon α to both a carboxylate and a phosphinyl group are largely absent, however. A rare example is that reported by Pietrusiewicz and coworkers[7] and shown in equation 1.

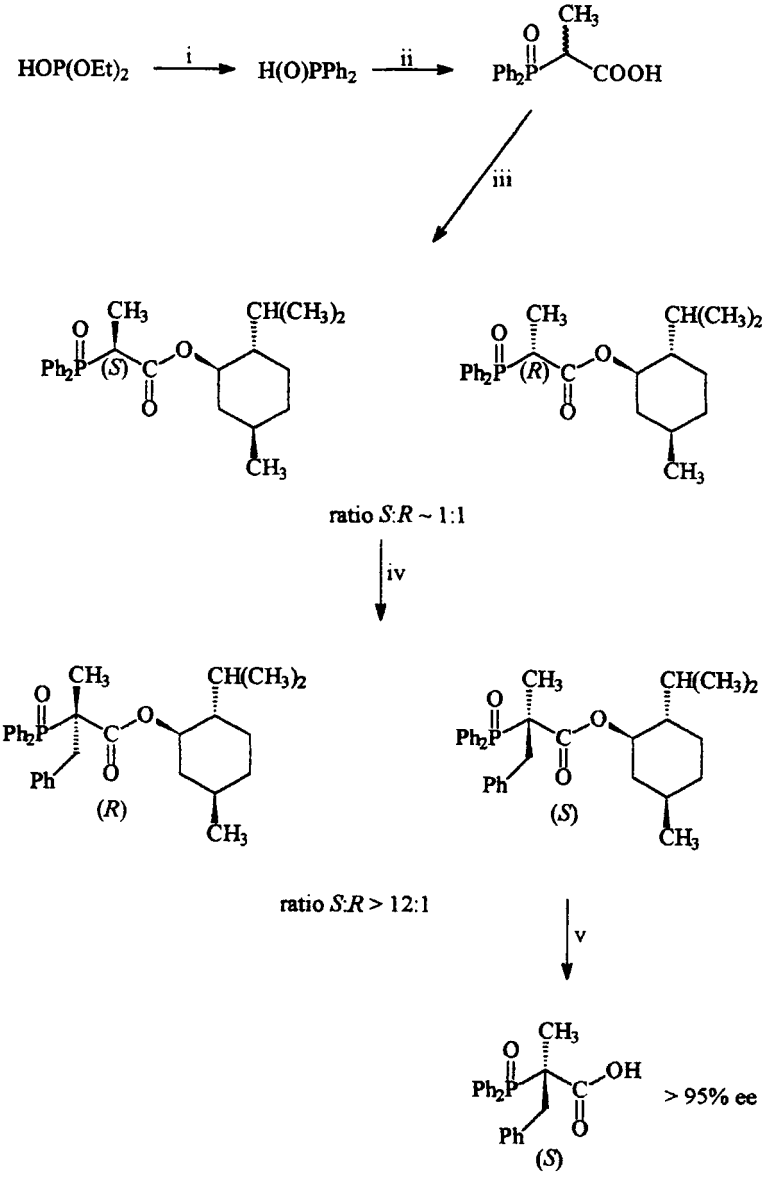


(-)-*R*(P) 2:1 diasteriomeric ratio (1)

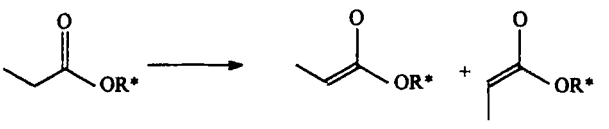
Scheme 1 outlines the steps in our synthesis. Although the single chiral auxiliary is the relatively distant (with respect to the nucleophilic carbon centre) ester function, it is sufficient to produce better than a 4:1 diasteriomeric mixture. A single chromatographic treatment enriched this beyond 12:1 and the subsequent ester cleavage produced the desired product at better than 95% ee.

The menthyl group is not easily removed from the menthyl 1-benzyl-1-(diphenylphosphinyl)propanoate because of steric crowding at the carbonyl centre (see also ref. 2). Standard base hydrolysis (aq. NaOH/thf) is ineffective, the ester being recovered intact. Treatment with 1M BBr_3 in CH_2Cl_2 proved to be successful, with the desired phosphinylcarboxylic acid being obtained in 70% overall yield.

A prerequisite of stereoselective enolate alkylation is the selective formation of one only of the two possible geometric isomers of the metallated anion **II** or **III**.

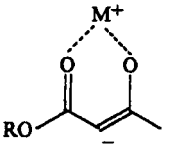


SCHEME 1 i) 2 PhMgBr; ii) $CH_3CH(Cl)CO_2H$, 50% aq. KOH / dmso; iii) *N*-methyl-2-bromopyridinium iodide, (1*R*, 2*S*, 5*R*)-menthol, DCM; iv) $Li(^iPr_2N)$, $PhCH_2Br$, thf, 24 l; v) 1M BBr_3 in DCM.



II III

The presence of a second donor such as the carbonyl function of a β-keto ester promotes the preferential formation of a single isomer, **IV**, by chelate stabilisation.



IV

The adoption of such a configuration is highly favoured with β-phosphinyl esters when the metal ion is lithium(I).[8] The menthyl group then determines the diastereoselectivity by favouring electrophilic attack at one face of the enolate-type anion, in our case the pro-*S* face. Menthyl and phen-menthyl esters have been used previously as chiral auxiliaries in asymmetric syntheses.[9]

Crystal Structure

Crystallisation of $Ph_2P(O)CMe(CH_2Ph)COOH$ from $MeOH/CHCl_3$ gave large colourless crystals suitable for x-ray analysis. A view of the molecule is shown in Figure 1, with salient bond lengths and angles collected in Table II. The absolute configuration of the chiral carbon is *S*. All pertinent bond lengths are within the expected range, including P=O, 1.496(2)Å; C=O, 1.198(3)Å and C-OH, 1.310(3)Å.

There is no intramolecular hydrogen bonding between the carboxylic hydrogen and the phospinyl oxygen, but strong intermolecular interactions between the carboxylate hydrogen of one molecule and the phosphinyl oxygen of a neighbouring molecule are apparent (Figure 2). The O2-O1_a distance is 2.567(3)Å, and the O-H·····O angle is 167(4)°. O1_a is related to O1 by the symmetry operator (-x, y + ½, ½ – z).

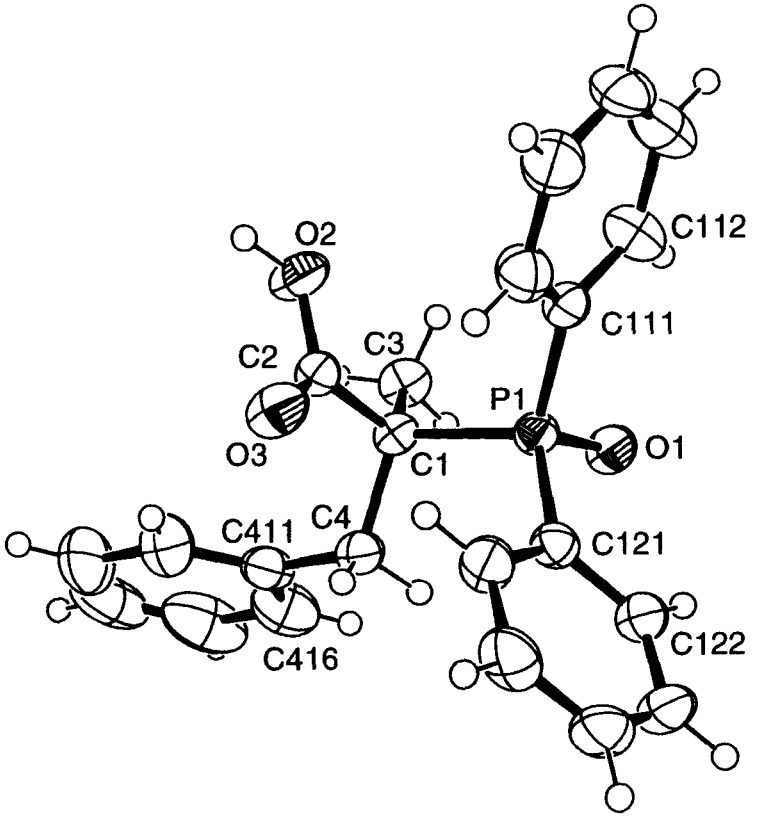


FIGURE 1 A view of the molecule

TABLE II Salient bond lengths(Å) and angles(°)

P(1) – O(1)	1.496(2)	C(2) – 0(3)	1.198(3)
P(1) – C(1)	1.863(2)	C(1) – C(2)	1.533(3)
P(1) – C(111)	1.813(2)	C(1) – C(3)	1.544(3)
P(1) – C(121)	1.812(2)	C(1) – C(4)	1.558(3)
C(2) – O(2)	1.310(3)	C(4) – C(411)	1.518(3)
O(1) – P(1) – C(111)	110.50(11)	O(2) – C(2) – O(3)	123.7(2)
O(1) – P(1) – C(121)	108.95(11)	0(2) – C(2) – C(1)	112.7(2)
O(1) – P(1) – C(1)	109.11(11)	O(3) – C(2) – C(1)	123.6(2)
P(1) – C(1) – C(2)	110.4(2)	C(3) – C(1) – C(4)	111.9(2)

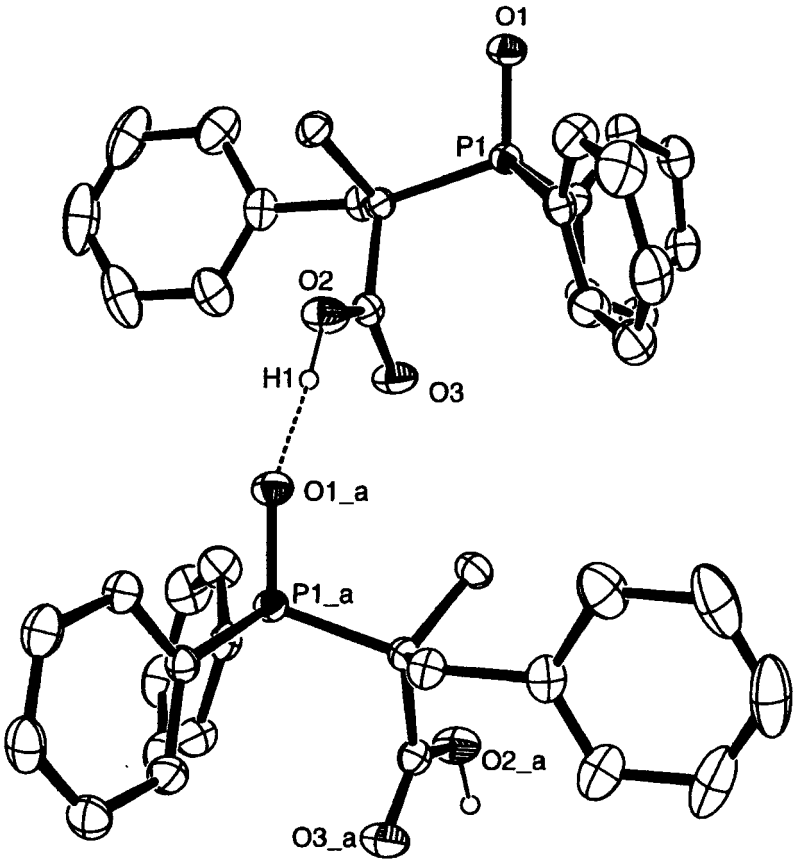


FIGURE 2 The strong intermolecular interactions between the carboxylate hydrogen of one molecule and the phosphinyl oxygen of the neighbouring molecule are shown

Acknowledgements

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