Synthetic and structural chemistry of enantiomerically pure 1-phenyl-2-carboxyethylphosphonic acid and its derivatives†

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(*S*)-(+)-1-Phenyl-2-carboxyethylphosphonic acid, (*S*)-**1**, has been prepared *via* diastereoselective alkylation of (3a*R*,7a*R*)-octahydro-1,2,3-tribenzyl-1,3,2-benzodiazaphosphole 2-oxide (**3**) using *tert*-butyl bromoacetate; the X-ray crystal structure of the intermediate alkylation product is described. The X-ray structure of a single crystal of (*R*)-**1**, obtained by crystallisation of *rac*-**1** is reported. The structure of (*R*)-**1** shows a three-dimensional pattern of intermolecular hydrogen bonding involving P(O)···HO–C, P–OH···(O)C and P(O)···HO–P interactions, but without any association between pairs of carboxyl groups. Attempts to resolve *rac*-**1** with various enantiomerically pure bases are reported. The X-ray structure of the hydrated double salt (*R*)-1-phenylethylammonium *rac*-1-phenyl-2-carboxyethylphosphonate hydrate is reported; this double salt crystallised unexpectedly from aqueous solutions of the product from *rac*-**1** and *rac*-1-phenylethylamine.

In recent years, there has been considerable interest in chemistry involving metal carboxyalkylphosphonates.[1] In particular, a number of layered metal phosphonates of the general type $[M_n\{O_3P(CH_2)_mCO_2H\}_x]_y$, *e.g.* $[Zr(O_3PCH_2CH_2CO_2H)_2]$,[2] and 3-D framework structures $[M_n\{O_3P(CH_2)_mCO_2\}_x]_y$, *e.g.* $[Co_3(O_3PC_2H_4CO_2)_2]$,[3] derived from the corresponding phosphonic acids have been described.

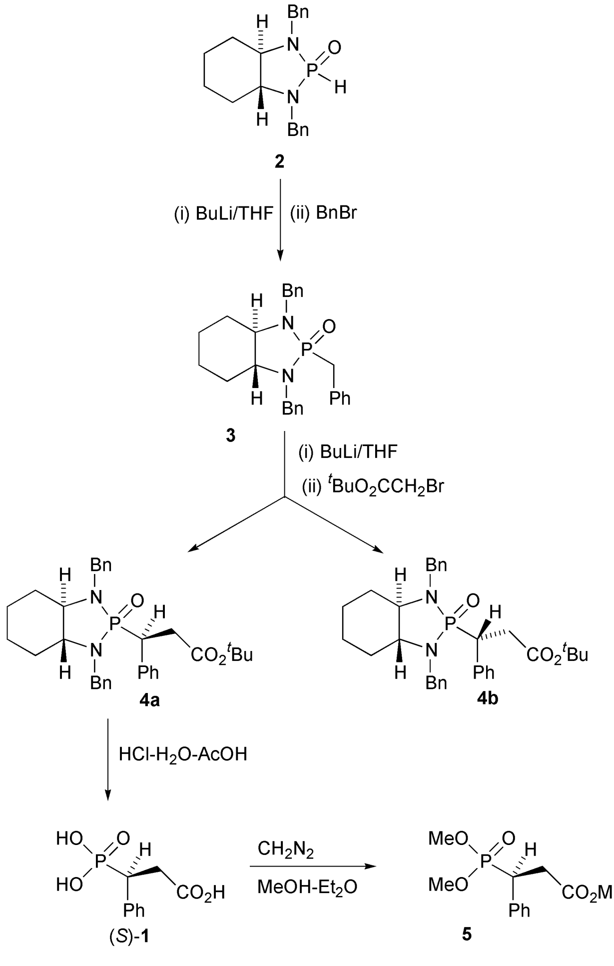
Similar metal phosphonates bearing sulfonic[4] and amino functions [5] have also been described. The intercalation chemistry[6] and catalytic properties[4] of some of these systems have been reported. It occurred to us that related carboxyalkylphosphonate materials bearing a chiral centre close to the carboxyl function might facilitate enantioselective chemistry from derived carboxyalkylphosphonates. To this end, we began to explore the chemistry of 1-phenyl-2-carboxyethylphosphonic acid, $(HO)_2P(O)CH(Ph)CH_2CO_2H$ (**1**) and its derivatives.

In this paper, we report on the asymmetric synthesis of the acid (*S*)-**1**, the structure determination of a single crystal of the enantiomer (*R*)-**1** by X-ray diffraction, the attempted resolution of *rac*-**1** using various bases and the crystal structure the double salt (*R*)-1-phenylethylammonium *rac*-1-phenyl-2-carboxyethylphosphonate (**6**), formed unexpectedly from *rac*-**1** and *rac*-1-phenylethylamine.

Results and discussion

Asymmetric synthesis of (*S*)-1-phenyl-2-carboxyethylphosphonic acid [(*S*)-1]

(*S*)-1-Phenyl-2-carboxyethylphosphonic acid, (*S*)-**1** was prepared by asymmetric synthesis, as shown in Scheme 1, using the general approach of Bennani and Hanessian.[7] The key step involved the electrophilic attack of *tert*-butyl bromoacetate on the stabilised carbanion generated by lithiation of the chiral bicyclic phosphonamide **3**. This led to the formation of the diastereoisomeric alkylation products **4a** and **4b** in a 93 : 7 ratio,



Scheme 1 Asymmetric synthesis of (*S*)-1-phenyl-2-carboxyethylphosphonic acid.

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† Electronic supplementary information (ESI) available: Tables S1–6. See http://www.rsc.org/suppdata/nj/b1/b111244a/

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as determined by ^{31}P NMR. As far as we are aware, this is the first example of the use of an α-haloester as a partner for reaction with a phosphonamide such as **3**, and it is further evidence of the versatility of both these classes of compound in the stereoselective formation of carbon–carbon bonds. The major product **4a** was isolated by chromatography, followed by crystallisation. A single crystal X-ray diffraction study (Fig. 1) confirmed the (*S*)-configuration of the new chiral centre, which was in accord with the model devised by Hanessian. Cleavage of both the phosphonamide chiral auxiliary and of the *tert*-butyl ester was then achieved by acid hydrolysis and the acid (*S*)-**1** was separated from the diamine chiral auxiliary by ion exchange chromatography. Acid (*S*)-**1** was shown to be enantiomerically pure by treatment with diazomethane to give the corresponding triester (*S*)-**5**; this was a single isomer by chiral HPLC [Chiralpak OT(+), hexane–isopropanol (9 : 1)] under conditions which were found to resolve the enantiomers of the racemic ester *rac*-**5**. Attempts to determine the ee of samples of ester **5** by both ^{31}P NMR (101 MHz) or ^{1}H NMR (250 MHz) spectroscopy in $CDCl_3$ and in the presence of the chiral shift reagent europium tris(trifluoroacetyl)-(+)-camphorate were frustrated because addition of relatively small amounts of the paramagnetic lanthanide complex produced severe line broadening without distinguishing between (*R*)-**5** and (*S*)-**5**.

Attempted resolution of racemic 1-phenyl-2-carboxyethylphosphonic acid (*rac*-1)

Racemic 1-phenyl-2-carboxyethylphosphonic acid, *rac*-**1**, was readily prepared on a multigram scale from the phosphonate ester obtained from conjugate addition of triethyl phosphite to *trans*-cinnamic acid, as described by Kamai and Kukhtim.[8] Treatment of the racemic diethyl 2-carbethoxy-1-phenylethylphosphonate ester with concentrated HCl gave *rac*-**1** in high yield.[9] Resolution through the formation of diastereomeric salts was then attempted by mixing ethanolic solutions of *rac*-**1** with a range of enantiomerically pure organic bases (0.5 equiv.). The resolving agents studied were (+)-cinchonine, (1*R*,2*S*)-(−)-norephedrine, (1*R*,2*S*)-(−)-ephedrine, (1*R*,2*S*)-(−)-*N*-methylephedrine, (1*R*,2*S*)-(+)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-ol, (*R*)-(+)-1-phenylethylamine, (*S*)-(−)-1-phenylethylamine, (−)-adrenaline, (1*R*,2*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine, (*S*)-(+)-leucinol and (−)-sparteine. Solid precipitates of salts were obtained only in the experiments using (1*R*,2*S*)-(−)-ephedrine, the enantiomeric 1-phenylethylamines and (−)-sparteine. ^{1}H and ^{31}P NMR spectroscopy did not distinguish between the pairs of diastereomeric salts formed in these experiments. For this reason, chiral HPLC was used to derive information regarding the extent of resolution. Thus the salts were first converted into the acid **1** using ion exchange chromatography and subsequently converted into the methyl esters **5** by treatment with diazomethane. HPLC on these esters revealed that 1-phenylethylamine and (−)-sparteine failed to resolve the acid to any significant extent (ee less than 5%). The salts with (−)-ephedrine on the other hand gave the ester (*R*)-**5** with 54% ee. The ephedrine salts of **1** were recrystallised from a mixture of glacial acetic acid and diethyl ether, and after five such recrystallisations the chemical yield of salt was 51%, based on ephedrine, and the ee of the derived ester (*R*)-**5** had increased to 81%.

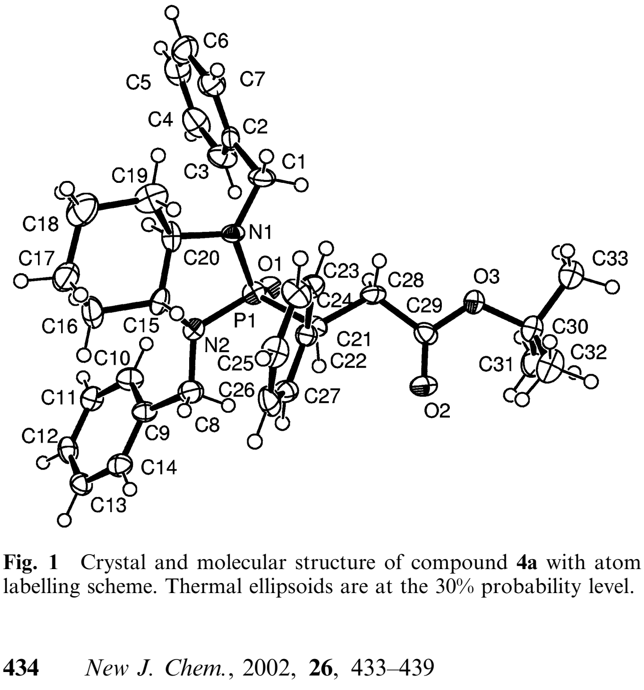

Fig. 1 Crystal and molecular structure of compound **4a** with atom labelling scheme. Thermal ellipsoids are at the 30% probability level.

Structural chemistry

Alkylation product 4a. A single crystal of (1′*S*,3a*R*,7a*R*)-1,3-dibenzyl-2-(1-phenyl-2-*tert*-butoxycarbonylethyl)octahydro-1,3,2-benzodiazaphosphole 2-oxide, **4a**, was obtained by dissolving **4a** in hot dichloromethane, then diluting the solution with diethyl ether and allowing it to cool. The structure is shown in Fig. 1. The absolute configuration was established using the knowledge that the benzodiazophosphole **2** had been prepared from (1*R*,2*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine.[10] Thus, it could be deduced that the chiral centre generated in the alkylation reaction had the (*S*)-configuration. The phosphorus atom has a distorted tetrahedral coordination, with the average of the six bond angles involving phosphorus being 109.3°. The smallest of these angles is N(1)–P(1)–N(2), which is inside the 5-membered ring and is only 94.2(3)°, whereas at the other extreme, the angle N(1)–P(1)–O(1) is 119.2(3)° (see Table S1, ESI). The geometry at the nitrogen atoms is flattened and the sums of the three bond angles centred on atoms N(1) and N(2) are 354.9 and 351.2°, respectively (360° would be required for complete planarity). These features are similar to those previously reported by Hanessian and co-workers[11] and by us[12] for related benzodiazophosphole structures, although the nitrogen geometry is somewhat flatter than usual; the sums of bond angles to nitrogen fall in the range 344.3–350.6° in ref. 11 and 12.

Crystal structure of (*R*)-1-phenyl-2-carboxyethylphosphonic acid [(*R*)-1]. Single crystals from *rac*-**1** were grown by slow evaporation of a saturated solution in water and acetone. The structure shows that the selected crystal contained purely the (*R*)-**1** enantiomer, as shown in Fig. 2, indicating that **1** crystallised as a conglomerate.

The structure exhibits a three-dimensional arrangement of stacked layers, the layers generated from hydrogen-bonded interactions between component acid units (Fig. 3). Within each layer, single tri-acid molecules are connected to three others by hydrogen bonding, the carboxylic acid fragment connected to one other molecule and the phosphonic acid fragment connected to two other molecules. The carboxylic acid fragment of each tri-acid molecule forms two hydrogen-bonded connections to the phosphonic acid end of a neighbouring molecule, generating an 8-membered ring. The P(O)···HO–C distance, at 1.718 Å, is significantly shorter than the P–OH···(O)C distance of 1.959 Å (Table S3, ESI). In addition to these intermolecular hydrogen bonds between phosphonic and carboxylic fragments, we also have symmetrical intermolecular 8-membered hydrogen-bonded ring connections, P(O)···HO–P, between the phosphonic acid fragments of two adjacent molecules. It is noteworthy that intermolecular associations between carboxylic acid groups are not seen in this supramolecular assembly. The intermolecular hydrogen bonding between the tri-acid molecules results in large inter-

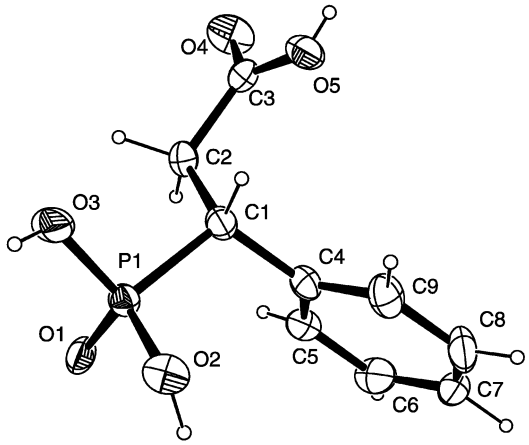

Fig. 2 Crystal and molecular structure of compound (*R*)-**1** with atom labelling scheme. Thermal ellipsoids are at the 30% probability level.

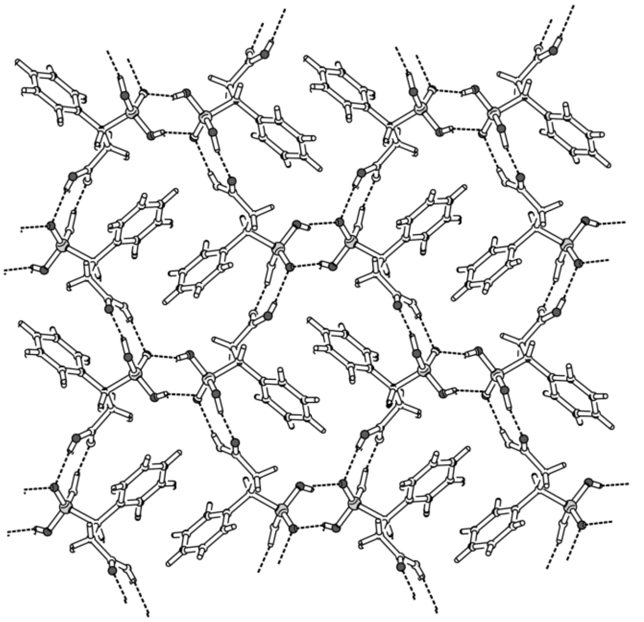

Fig. 3 Hydrogen bonding in (*R*)-**1** within a single layer.

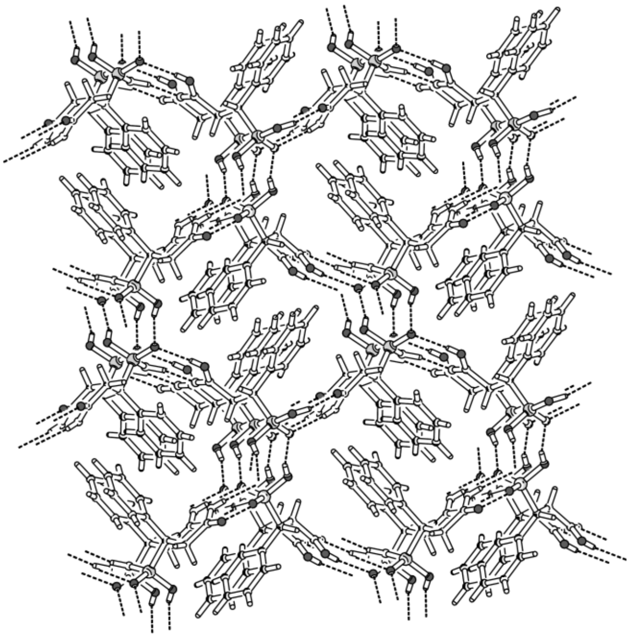

Fig. 4 Diagram showing the stacking in structure (*R*)-**1**.

connected ring structures, with each ring containing six hydrogen-bonded interactions of the type already described involving six different acid molecules, Fig. 3. In this arrangement, each tri-acid molecule is shared between three connected ring structures, being surrounded by six identical rings. Each of these rings accommodates two phenyl groups of two of the component acid molecules. In the three-dimensional picture, Fig. 4, the layers are arranged such that these larger ring structures are stacked, generating channels with stacked phenyl π-systems and much smaller channels based on stacked 8-membered ring hydrogen bonds between ring components. While there are no other structurally characterised carboxyalkyl phosphonic acid systems having an in-built chiral centre, the structures of two other carboxyalkyl phosphonic acids, namely phosphonoacetic acid, $(HO)_2P(O)CH_2COOH$, and 2-(phosphonomethyl)acrylic acid hemihydrate, $(HO)_2P(O)CH_2C(CH_2)COOH\cdot0.5H_2O$, have been reported.[13,14] One interesting aspect not mentioned in the original report is that although an isolated molecule of $(HO)_2P(O)CH_2COOH$ would be achiral, the hydrogen bonding in the solid state effectively generates a chiral centre at each phosphorus atom, so that the crystal itself is chiral. Whereas each tri-acid in (*R*)-**1** is hydrogen bonded to three other tri-acid molecules, in $(HO)_2P(O)CH_2COOH$ each tri-acid forms hydrogen bonds to six other molecules, resulting in a more densely packed structure. Bond distances and angles in (*R*)-**1** are given in Table S2 (ESI) and are generally comparable with those reported for $(HO)_2P(O)CH_2COOH$. The tri-acid (*R*)-**1** displays slightly distorted tetrahedral geometry at phosphorus, C(1) and C(2). The angles around C(3) range from 114.2(5)–124.8(5)° and their sum is 359.9°.

Crystal structure of (*R*)-1-phenylethylammonium *rac*-1-phenyl-2-carboxyethylphosphonate hydrate (6·H₂O). The reaction between *rac*-**1** and *rac*-1-phenylethylamine in water gave a white precipitate. X-Ray quality crystals of **6**·H_2O were obtained upon recrystallisation from water. The asymmetric unit is shown in Fig. 5 and consists of two (*R*)-**1**-phenylethylammonium cations, two 1-phenyl-2-carboxyethylphosphonate anions and two water molecules. Attempts to solve the structure in the higher symmetry space group $P2_1/c$ as the racemic salt required imposed 50 : 50 disorder at the chiral carbon in the ammonium cation and resulted in a higher *R*-factor (by 2%) for the structure. The structure solution in the $P2_1$ space

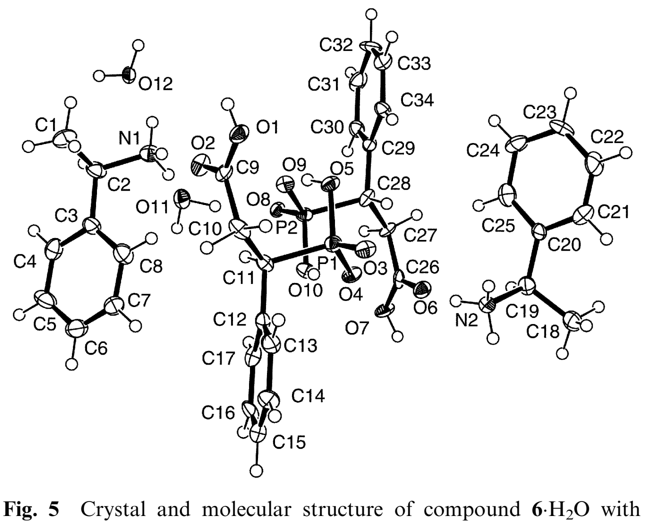

Fig. 5 Crystal and molecular structure of compound **6**·H_2O with atom labelling scheme. Thermal ellipsoids are at the 30% probability level.

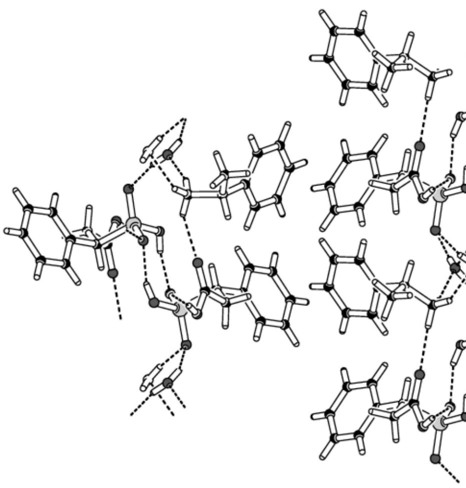

Fig. 6 Hydrogen bonding in $6 \cdot H_2O$ within a single layer.

group is considered to be the correct one. The formation of the double salt in preference to a racemate explains the failure of enantiomerically pure 1-phenylethylamine to effect any resolution of *rac*-**1**. Double salt formation from acid–base combinations has been seen in cases where one of these is a single enantiomer and the other is racemic.[15,16] However, structurally characterised examples are apparently rare. A reported example is (*S*)-1-phenylethylammonium 4-cyano-2-ethyl-2-(4-nitrophenyl)butanoate[17] and the phenomenon is discussed in ref. 15. In contrast to those double salts previously discussed, compound **6** was prepared from the racemic acid and base. It is noteworthy that this possible outcome has previously been overlooked in a very extensive study of such reactions.[16] It is known that conglomerate formation is often favoured in the reactions of racemic amines with achiral mono and dicarboxylic acids.[18] In this respect, compound $\mathbf{6} \cdot H_2O$ shows a relevant structural feature with hydrogen-bonded (*R*)–(*S*) dimers of the anions containing a local centre of inversion (Fig. 5). The H-bonded network in the double salt generates columns of alternating phosphonate anions and ammonium cations. The anions and cations within the column are related by a two-fold screw axis, as was found to be the case for conglomerates from chiral amines and achiral carboxylic acids.[18]

There is tetrahedral geometry about phosphorus [range 105.0(3)–115.9(3)°] and nitrogen (Table 4, ESI). The distortion from planar geometry at the carboxylic carbon atom is reflected in the angles 112.0(6), 123.2(7), 124.8(7), the smallest due to HO–C(O)–C–, and is likely imposed by packing forces. Anions and cations within the columns are arranged firstly in hydrogen-bonded layers (Fig. 6) consisting of 8-membered rings between neighbouring phosphonates, P(O)···H–OP, as well as interactions between phosphonate and water P(O)···HOH, ammonium and carbonyl sites $-NH_3^+ \cdots (O)C(OH)-$, and ammonium and water $-NH_3^+ \cdots OH_2$. The layers are connected by hydrogen bonds between phosphonate and carboxylic acid, P(O)···HOC(O) (Fig. 7; Table S5, ESI).

Conclusions

The acid **1** has been prepared in enantiomerically pure form for the first time, using an asymmetric alkylation reaction, and the absolute configuration has been determined. A partial classical resolution of **1** has also been achieved, but success here is critically dependent on a suitable choice of resolving agent. In the case of reaction with *rac*-phenylethylamine, the isolation of a double salt revealed an unexpected type of selectivity and the double salt shows similar structural features to conglomerates from chiral amines and achiral carboxylic acids.[18] The crystal structure of **1** reveals a remarkable network of hydrogen bonding. Either the acid **1** or its metal salts may be of interest as chiral solid acid catalysts for organic reactions.

Experimental

Materials and general procedures

All reactions involving BuLi were conducted under a nitrogen atmosphere. Racemic diethyl 2-carbethoxy-1-phenylethylphosphonate was prepared according to the literature[8] and converted to the corresponding tri-acid *rac*-**1** by treatment with conc. HCl.[9]

Preparation of (3a*R*,7a*R*)-octahydro-1,2,3-tribenzyl-1,3,2-benzodiazaphosphole 2-oxide (3)

(3a*R*,7a*R*)-Octahydro-1,3-dibenzyl-1,3,2-benzodiazaphosphole 2-oxide (**2**)[10] (1.67 g, 4.90 mmol) in THF (20 ml) was cooled to −78 °C and treated with 1.6 M BuLi in hexane (3.2 ml, 5.1 mmol). The orange solution was maintained at −78 °C for 40 min, then benzyl bromide (0.583 ml, 4.91 mmol) was added

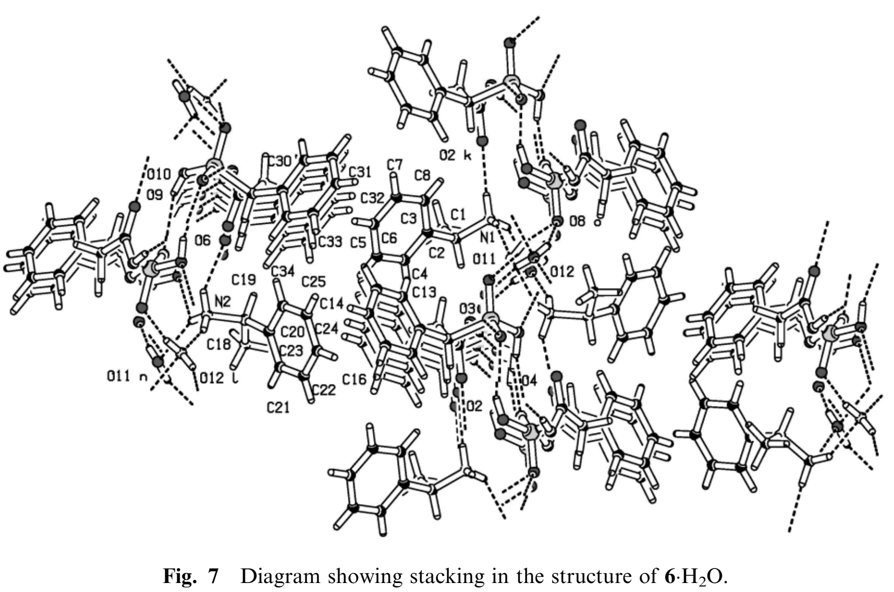

Fig. 7 Diagram showing stacking in the structure of $\mathbf{6} \cdot H_2O$.

and the cooling bath was allowed to warm up to room temperature over 80 min. Saturated aqueous NH_4Cl (5 ml) was added and the mixture was partitioned between CH_2Cl_2 (100 ml) and H_2O (50 ml). The organic phase was washed with water (2 × 50 ml), dried ($MgSO_4$) and the solvent evaporated to leave a residue which was purified by flash chromatography [CH_2Cl_2–Et_2O (9 : 1)] followed by recrystallisation (CH_2Cl_2–Et_2O) to yield **3** (0.86 g, 41%) as fluffy white needles, mp 124.5–125.5 °C, $[\alpha]^{29}_D$ −53.1 (*c* 1.0, CH_2Cl_2). Found: C, 75.1; H, 7.3; N, 6.5; $C_{27}H_{31}N_2OP$ requires C, 75.3; H, 7.3; N, 6.5%. δ_P (109 MHz; $CDCl_3$) 40.0 [lit.[19] for *rac*-(**3**) δ_P +39.9].

Preparation of (1′*S*,3a*R*,7a*R*)-1,3-dibenzyl-2-(1-phenyl-2-*tert*-butoxycarbonylethyl)octahydro-1,3,2-benzodiazaphosphole 2-oxide (4a)

A solution of **3** (333 mg, 0.77 mmol) in dry THF (7 ml) at −100 °C was treated with 1.6 M BuLi in hexane (0.53 ml, 0.85 mmol) and the resulting orange solution was stirred at −100 °C for 20 min. *tert*-Butyl bromoacetate (126 μl, 0.85 mmol) was then added and, after a further 30 min at −100 °C followed by 1 h at −80 °C, the reaction mixture was quenched by addition of aqueous NH_4Cl (3 ml) and warmed to room temperature. The mixture was partitioned between CH_2Cl_2 (25 ml) and water (25 ml), then the CH_2Cl_2 layer was washed with a further portion of H_2O (25 ml), dried ($MgSO_4$) and the solvent evaporated to yield a colourless foam (419 mg). On the basis of ^1H and ^{31}P NMR spectroscopy, this crude product was considered to contain a mixture of unreacted starting material **3** [δ_P ($CDCl_3$) 40.0] and the two diastereoisomeric alkylation products **4a** [δ_P($CDCl_3$) 41.0] and **4b** [δ_P ($CDCl_3$) 39.6] in the molar ratio 22 : 73 : 5. Flash chromatography [CH_2Cl_2–Et_2O (96 : 4)] followed by recrystallisation from CH_2Cl_2–Et_2O–petroleum ether (40–60) gave **4a** (230 mg, 55%) as white crystals whose relative configuration was established by X-ray diffraction (Fig. 1), mp 180–180.5 °C, $[\alpha]^{29}_D$ −31.8 (*c* 1.1, CH_2Cl_2). Found C, 72.9; H, 7.8; N, 5.1; $C_{33}H_{41}N_2O_3P$ requires C, 72.8; H, 7.6; N, 5.1%. δ_H (250 MHz; $CDCl_3$) 0.66–0.95 (4 H, m, cyclohexyl-H_4), 1.21 (9 H, s, ^{t}Bu), 1.28–1.49 (3 H, m, cyclohexyl-H_3), 1.68–1.70 (1 H, m, cyclohexyl-H), 1.90–2.00 (1 H, m, 3a- or 7a-H), 2.57 (1 H, td, *J* 10 and 3, 7a- or 3a-H), 2.69 (1 H, ddd, *J* 16, 12 and 7, C*H*$CO_2{}^t$Bu), 3.07 (1 H, ddd, *J*16, 8 and 4, C*H*$CO_2{}^t$Bu), 3.68–3.86 (2 H, m, PhC*H*P and PhC*H*N), 4.07 (1 H, dd, *J* 15 and 10, PhC*H*N), 4.18 (1 H, t, *J* 15, PhC*H*N), 4.50 (1 H, dd, *J* 16 and 10 Hz, PhC*H*N) and 7.16–7.53 (15 H, m, 3 × Ph); δ_C (101 MHz, $CDCl_3$) 24.0 (cyclohexyl), 24.3 (cyclohexyl), 27.8 (C*Me*$_3$), 28.9 (d, $^3J_{PC}$ 9, cyclohexyl), 29.6 (d, $^3J_{PC}$ 7, cyclohexyl), 36.9 (*C*H_2CO), 43.9 (d, $^1J_{PC}$ 110, *C*HP), 46.5 (d, $^2J_{PC}$ 5, cyclohexyl), 48.6 (d, $^2J_{PC}$ 2, cyclohexyl), 63.2 (d, *J* 5, *C*H_2Ph), 63.6 (d, *J* 8, *C*H_2Ph), 80.6 (*C*Me_3), 126.9, 127.1 (d, *J* 3), 127.29, 127.34, 128.01 (d, *J* 3), 128.2, 128.4, 129.0, 129.7 (d, *J* 5), 136.8 (d, *J* 6), 137.7 (d, *J* 2), 140.6 (d, *J* 4) and 170.4 (d, $^3J_{PC}$ 20 Hz, CO); δ_P (109 MHz, $CDCl_3$) 41.0. MS (FAB) *m*/*z* found: MH^+, 545.2950; $C_{33}H_{42}N_2O_3P$ requires 545.2933.

Preparation of (*S*)-1-phenyl-2-carboxyethylphosphonic acid [(*S*)-1] by hydrolysis of 4a

4a (34.0 mg, 0.062 mmol) was dissolved in acetic acid (1 ml), then concentrated HCl (1 ml) was added. The mixture was heated at 75 °C for 14 h and the water was then evaporated. The residue was re-dissolved in water, which was then evaporated, and the solid applied to a 1.5 × 15 cm column of Dowex 50W-X8(H) ion exchange resin. Elution with water, followed by evaporation of the water and drying *in vacuo* over P_2O_5 gave (*S*)-**1** (13.8 mg, 96%) as a white solid, mp 208–210 °C, $[\alpha]^{31}_D$ +13 (*c* 0.85, H_2O). Found: C, 46.8; H, 4.8; $C_9H_{11}O_5P$ requires C, 47.0; H, 4.8%. δ_H (250 MHz, D_2O) 3.17 (1 H, ddd, *J* 16, 11 and 9, C*H*CO_2H), 3.28 (1 H, ddd, *J* 16, 9 and 5, C*H*CO_2H), 3.67 (1 H, ddd, *J* 22, 11 and 5 Hz, PhC*H*) and 7.45–7.6 (5 H, m, Ph).

Determination of the enantiomeric excess of 1

rac-**1** (200 mg) was dissolved in methanol (10 ml) and treated with a solution of diazomethane in diethyl ether until a persistent yellow colour was seen. The solvents and excess diazomethane were evaporated to leave the trimethyl ester of *rac*-1-phenyl-2-carboxyethylphosphonic acid (*rac*-**5**) (225 mg, 95%) as an oil. ν_{max} (film) 1740 cm^{-1}. δ_H (250 MHz; $CDCl_3$) 2.87–3.15 (2 H, m, CH_2CO), 3.51 (3 H, d, *J* 10.5, MeOP), 3.58 (3 H, s CO_2Me), 3.60–3.76 (1 H, m, CHP), 3.69 (3 H, d, *J* 11 Hz, MeOP) and 7.22–7.39 (5 H, m, Ph); δ_P (109 MHz; $CDCl_3$) 31.5. MS (FAB) *m*/*z* found: MH^+, 273.0901; $C_{12}H_{18}O_5P$ requires 273.0892. HPLC [4.6 × 250 mm Chiralpak OT(+) column; hexane–isopropanol (9 : 1); 12 °C; flow rate 1 ml min^{-1}]: absorbance measurements at 254 nm showed peaks of equal area with retention times of 13.0 and 14.2 min.

A sample of (*S*)-**1** obtained by hydrolysis of **4a** was similarly converted into the trimethyl ester (*S*)-**5**, which showed a single enantiomer of retention time 13.0 min when analysed by HPLC under the above conditions.

Preparation of (*R*)-1-phenylethylammonium *rac*-1-phenyl-2-carboxyethylphosphonate (6·H_2O)

rac-1-Phenylethylamine (0.5 ml, 4.34 mmol) was added to a solution of *rac*-**1** (1.00g, 4.34 mmol) in distilled water (60 ml) and the mixture stirred for 5 days. After evaporation of the water to approximately 5 ml, a white precipitate appeared. This was dried by suction filtration and recrystallised from distilled water to give *rac*-[NH_3CHCH_3Ph][$O_2P(OH)CHPhCH_2$-CO_2H]·H_2O as colourless crystals (1.46 g, 91%), mp 195–198 °C.

The *rac*-(1-phenylethylammonium 1-phenyl-2-carboxyethylphosphonate) obtained was composed in part of single crystals of **6**·H_2O.

Attempted resolution of *rac*-1 using (*R*)-(+)-1-phenylethylamine

(*R*)-(+)-1-Phenylethylamine (0.25 ml, 2.17 mmol) was added to a solution of *rac*-**1** (1.00g, 4.34 mmol) in distilled water (10 ml) and the mixture stirred for 12 h. The white precipitate was dried by suction filtration and recrystallised from distilled water to give (*R*)-[NH_3CHCH_3Ph]-*rac*-[$O_2P(OH)CHPhCH_2$-COOH]·H_2O as colourless crystals (0.26 g, 32%), mp 195–198 °C. Found C, 55.05; H, 6.5; N, 3.7; P, 8.6; $C_{17}H_{24}NO_6P$ requires C, 55.3; H, 6.6; N, 3.8; P, 8.4%. δ_H (270 MHz; D_2O) 1.64 (d, *J* 7 Hz, 3H, CH_3), 3.08 (m, 2H, CH_2), 3.43 (m, 1H, PCH), 4.53 (q, *J* 7, 1H, NCH), 7.48 (m, 5H, Ph), 7.36 (m, 5H, Ph); δ_C (68 MHz; D_2O) 19.46 (CH_3), 35.78 (CH_2), 42.74 (d, PCH, $^1J_{PC}$ 130), 51.17 (NCH), 126.66, 126.97, 128.70, 128.79, 129.34, 129.43, 137.91, 138.29 [d, C_6H_5CHP (*ipso*-C), $^2J_{PC}$ 7], 176.81 (d, CO_2H, $^3J_{PC}$ 19 Hz); δ_P (109 MHz; D_2O) 25.3 (s).

Ion exchange of this sample with Dowex 50W-X2 (H^+ form) afforded 1-phenyl-2-carboxyethylphosphonic acid which was essentially racemic, as determined by conversion into the methyl ester with CH_2N_2, followed by chiral HPLC analysis.

Similar results were obtained when the salt of *rac*-**1** with (*S*)-(−)-phenylethylamine was precipitated from ethanol solution and recrystallised twice more from EtOH (yield of salt = 30%; 30%; ee of derived acid **1** < 5%).

Table 1 X-ray data

Compound	**4a**	(*R*)-**1**	**6**·H_2O
Empirical formula	$C_{33}H_{41}N_2O_3P$	$C_9H_{11}O_5P$	$C_{17}H_{24}NO_6P$
Formula weight	544.65	230.15	369.34
Temperature/K	160(2)	120(2)	120(2)
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Unit cell dimensions	$a = 10.716(2)$ Å	$a = 5.671(1)$ Å	$a = 7.3857(2)$ Å
	$b = 10.737(2)$ Å	$b = 12.779(2)$ Å	$b = 25.4539(1)$ Å
	$c = 26.151(4)$ Å	$c = 14.064(3)$ Å	$c = 9.5109(4)$ Å
	$\alpha = \beta = \gamma = 90°$	$\alpha = \beta = \gamma = 90°$	$\alpha = \gamma = 90°$
			$\beta = 93.872(3)°$
Volume/Å^3	3008.9(9)	1019.2(3)	1783.92(11)
Z	4	4	4
Density/Mg m^{-3}	1.202	1.500	1.375
Absorption coefficient/mm^{-1}	0.127	0.268	0.187
Reflections collected	3082	2053	7503
Independent reflections	2996 [*R*(int) = 0.0052]	1788 [*R*(int) = 0.0581]	5690 [*R*(int) = 0.0518]
Final *R* indices [$I > 2\sigma(I)$]: *R*1, *wR*2	0.0555, 0.1003	0.0560, 0.1342	0.0587, 0.0965
R indices (all data): *R*1, *wR*2	0.2081, 0.1381	0.1085, 0.1567	0.1234, 0.1164

Partial resolution of 1-phenyl-2-carboxyethylphosphonic acid using (1*R*,2*S*)-(−)-ephedrine

rac-1-Phenyl-2-carboxyethylphosphonic acid (*rac*-**1**) (464 mg, 2.02 mmol) was dissolved in boiling EtOH (20 ml) and treated with a hot solution of (−)-(1*R*,2*S*)-ephedrine (167 mg, 1.01 mmol) in ethanol (10 ml). The mixture was allowed to cool slowly to room temperature before being placed in a freezer at −18 °C. The white crystals were filtered off, washed with cold EtOH, followed by Et_2O, and dried to give the (−)-ephedrine salts of the enantiomeric 1-phenyl-2-carboxyethylphosphonic acids (360 mg, 90% yield based on ephedrine; 54% de in favour of the (*R*)-acid as determined by ion exchange on Dowex 50W-X8(H), treatment with diazomethane and chiral HPLC). A portion (269 mg) of this salt was dissolved in hot glacial acetic acid (4 ml); the solution was cooled to room temperature and Et_2O (16 ml) was added, whereupon crystals formed. The mixture was cooled to 4 °C and the mother liquors were decanted from the crystals, which were washed with Et_2O and subjected to four further recrystallisations from AcOH–Et_2O. The crystals were ground and dried at 90 °C and 0.5 mmHg to give the (1*R*,2*S*)-ephedrine salts of the enantiomeric 3-phenyl-3-phosphonopropanoic acids (155 mg, 51% yield based on ephedrine; 81% ee in favour of the (*R*)-acid as determined by ion exchange, treatment with diazomethane and chiral HPLC), mp 203–207 °C. Found: C, 56.3; H, 6.6; N, 3.4; $C_{19}H_{26}NO_6P \cdot 0.5H_2O$ requires C, 56.4; H, 6.7; N, 3.4%. δ_H (250 MHz; DMSO-d_6) 0.86 (3 H, d, *J* 7, CH*Me*), 2.51 (3H, s, NMe), 2.46–2.62 (1 H, m, CHP), 2.91–3.10 (2 H, m, C$H_2$$CO_2$H), 3.21 (qd, *J* 7 and 2, C*H*Me), 5.05 (1 H, d, *J* 2 Hz, PhCHO) and 7.07–7.38 (10 H, m, 2 × Ph); δ_P (109 MHz; DMSO-d_6) 19.4.

X-Ray crystallography

Data for (*R*)-**1** and **4a** were collected at 160 K on a CAD4 diffractometer using Mo-Kα ($\lambda = 0.71069$ Å) radiation using $\omega - 2\theta$ scans and corrected for absorption (Table 1).[20]

Data for **6**·H_2O were collected at 120 K using a Nonius Kappa CCD area detector diffractometer mounted at the window of a molybdenum rotating anode (50 KV, 90 mA, $\lambda = 0.71069$ Å). The crystal-to-detector distance was 45 mm and ϕ and Ω scans (0.7° increments, 84 s exposure time) were carried out to fill the Ewald sphere. Data collection and processing were carried out using the programs COLLECT,[21] DENZO[22] and maXus[23] and empirical absorption correction was applied using SORTAV.[24] The structure was solved by direct methods using DIRDIF99[25] and refined anisotropically (non-hydrogen atoms) by full-matrix least-squares on F^2 using the SHELXL-97 program.[26] The H atoms were calculated geometrically and refined with a riding model. The program ORTEP-3[27] was used for drawing the molecules. WINGX[28] was used to prepare material for publication.

Hydrogen-bonding packing diagrams were generated using PLATON.[29]

CCDC reference numbers 177846–177848. See http://www.rsc.org/suppdata/nj/b1/b111244a/ for crystallographic data in CIF or other electronic format.

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