A synthesis of oligomeric α-hydroxy phenylphosphinates and a study of the conformational preferences of the dimers†

Kamyar Afarinkia,*[a] Martin Royappa,[a] Ian J. Scowen,[b] Jonathan W. Steed[c] and Hiu-wan Yu[a]

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A general method for the synthesis of a novel class of oligomers, comprising α-hydroxy phenylphosphinic acid building blocks, is reported. A series of dimeric α-hydroxy phenylphosphinates are analyzed by a combination of NMR spectroscopy, X-ray crystallography and computational methods.

Introduction

Many oligomeric organic macromolecules exhibit chemical and physical properties which exceed those expected from the combined properties of their individual constituents. A manifestation of this principle is in the ability of peptides and proteins to play key roles in biological events such as molecular recognition and catalysis. The reason that nature, at least on Earth, has chosen oligomers of α-amino carboxylic acids for this role has been actively pursued in the chemical literature.[1] At the same time, there has been a concerted effort to find other oligomeric macromolecules whose supramolecular properties can be exploited. The key structural feature sought in these oligomers is the predictable and repeating patterns of folding (secondary structure); stabilised by non-covalent bonding interactions, such as hydrogen bonding (H-bonding), enabling the macromolecule to adopt a specific shape. Indeed, the term *foldamer* has been coined by Gellman to specifically refer to such oligomers.[2a] In particular, syntheses and folding patterns of poly β-amino carboxylic acids,[2] polymers of non-natural α-amino carboxylic acids[3] and abiotic foldamers[4] have been extensively studied.

We have recently initiated an investigation into the preparation and supramolecular properties/folding patterns of oligomeric α-amino and α-hydroxy phosphonic/phosphinic acids. Although phosphonic and phosphinic acids have been recognized as the closest structural mimics of carboxylic acids for over 30 years,[5] no study of the suprastructure or conformational preferences of oligomeric α-amino and α-hydroxy phosphonic/phosphinic acids has been conducted previously. This is in spite the fact that small pseudo-peptides containing phosphonic and phosphinic acids have extensive medicinal applications.[6] The main reason for this appears to be the lack of convenient and efficient methods for the synthesis of these oligomers.[6a]

In this paper, we report a novel, general and highly efficient synthetic route to oligomers of α-hydroxy phenylphosphinic acids. In addition, we demonstrate that in a series of dimeric compounds, the propensity for intramolecular hydrogen bonding, a key requirement for folding, depends on the relative configuration of carbon and phosphorus stereocenters.

Results & discussions

Treatment of ethyl phenylphosphonite **1** with 3-methyl-2-butenal **2** afforded a 1 : 1 diastereomeric mixture of α-hydroxy phenylphosphinate **3a** and **3b** from which the latter was isolated as a crystalline solid (Scheme 1).

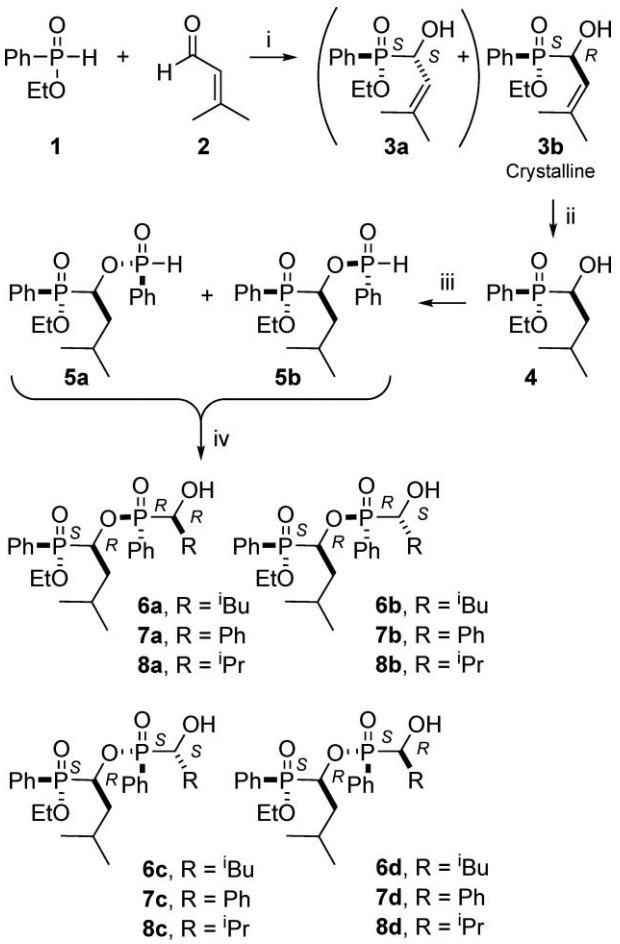
Relative configuration of **3b** was established by crystallography as the (S_P,R_C) diastereomer. Hydrogenation of **3b** afforded **4** which was then transformed into its corresponding chloroformate and subjected to the Hewitt reaction[7] to afford phenylphosphinates **5a** and **5b** also as a diastereomeric mixture (Scheme 1). The key feature of the Hewitt reaction is that the configuration of the carbon atom bearing the hydroxyl function is retained.[7b] Thus compound **5** is obtained as a diastereomeric mixture of (S_P,R_C,S_P) and (S_P,R_C,R_P) relative configurations. However, separation of the diastereomers proved to be impractical since the two are interconvertible due to $\sigma^3\lambda^3$–$\sigma^4\lambda^5$ tautomerism[8] of H-phosphinates/phosphonites. Treatment of compound **5** with isovaleraldehyde in a phospha-aldol reaction[9] then afforded a mixture of four diastereomeric dimers, **6a** (R_f(tlc) = 0.7 in ether), **6b** (R_f(tlc) = 0.4 in ether), **6c** (R_f(tlc) = 0.25 in ether) and **6d** (R_f(tlc) = 0.24 in ether). The diastereomers were separated by a combination of chromatography and crystallization. Similarly, treatment of compound **5** with benzaldehyde and isobutyraldehyde afforded diastereomers **7a–d** and diastereomers **8a–d** respectively.

We then set out to analyze the solution structure of diastereomers of the same series by NMR spectroscopy including $^1H\{^{31}P\}$ spectroscopy, NOESY (Nuclear Overhauser Enhancement Spectroscopy), and HOESY (Heteronuclear Overhauser Enhancement Spectroscopy) between phosphorus and hydrogen nuclei.

From the detailed study of these ^1H NMR spectra, it became clear that two of the diastereomers, **6a** and **6b**, had a different conformation from the other two **6c** and **6d** (copies of the spectra are provided in the ESI†). For instance, comparing

[a]*Institute of Cancer Therapeutics, Thumbling Hill Street, Bradford, UK BD7 1DP. E-mail: k.afarinkia@bradford.ac.uk; Fax: +44 (0)1274 233234; Tel: +44 (0)1274 235831*
[b]*Analytical Center, University of Bradford, Bradford, UK BD7 1DP. E-mail: i.scowen@bradford.ac.uk; Fax: +44 (0)1274 233234; Tel: +44 (0)1274 23619*
[c]*Department of Chemistry, University of Durham, Durham, UK DH1 3LE. E-mail: jon.steed@durham.ac.uk; Tel: +44 (0)191 33 42085*

† Electronic supplementary information (ESI) available: Experimental procedures for preparation of compounds **7a–d**, **8a–d**, **9a–b** and **10a–d**. Copies of proton, phosphorus and carbon NMR spectra. CCDC reference numbers 745848–745850 and 748564. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b917737j



Scheme 1 (i) 3-Methylbut-2-enal, KF; (ii) H_2, Pd/C, EtOAc; (iii) pyridine, $(COCl_2)_3$, CH_2Cl_2, 0 °C then $PhP(OH)_2$, reflux; (iv) Et_3N, TMSCl, CH_2Cl_2, 0 °C, then RCHO.

^{31}P-coupled and ^{31}P-decoupled ^{1}H spectra (^{1}H{^{31}P}) it is clear that in both diastereomers **6a** and **6b** the hydroxyl hydrogen (O*H*) is coupled to a hydrogen nucleus (H_β) and *both* phosphorus nuclei. Furthermore, HOESY between phosphorus and hydrogen nuclei clearly demonstrated that hydroxyl hydrogen (O*H*) is coupled slightly more strongly to the phosphorus nucleus bonded furthest away from it (P_α) than it is coupled to the phosphorus nucleus bonded closest to it (P_β) (see ESI†). In contrast, a similar study of the ^{1}H NMR and ^{31}P NMR spectra of diastereomers **6c** and **6d** showed that in these two diastereomers, the hydroxyl hydrogen (O*H*) is coupled to a hydrogen nucleus (H_β) and the phosphorus nucleus bonded closest to it only (P_β). Taken together, these observations suggest that the coupling between hydroxyl hydrogen, O*H*, and P_α in diastereomers **6a** and **6b** cannot be through-bond but must be through-space, the most likely form of which would be intramolecular hydrogen bonding. The possibility that the coupling might have arisen because of intermolecular hydrogen bonding was disregarded since successive ten-fold dilutions, until the limits of detection by NMR was reached, did not alter the spectra at all. We also made similar observations of a difference in properties between diastereomeric pairs in the other series, **7a–d** and **8a–d**.

To examine the propensity of compounds **6a–d** to form intramolecular hydrogen bonds from a theoretical perspective, we carried out a systematic search of their conformational preferences.[10] The results of these computations are shown below (Table 1). Starting from four different starting conformations, 1296 random conformations were analysed. In each case, lowest energy conformations were visually inspected. In two cases, diastereomers (S_P,R_C,R_P,S_C) and (S_P,R_C,R_P,R_C), the lowest energy conformation as well as a number of other low energy conformations were found to contain an intramolecular hydrogen bond between the hydrogen atom of the terminal hydroxyl group and the oxo atom (P=*O*) furthest away from it. In both cases, the conformations without this hydrogen bond were, as expected, higher in energy by at least 4 Kcal mol^{-1}. In the other two cases, diastereomers (S_P,R_C,S_P,S_C) and (S_P,R_C,S_P,R_C), the lowest energy conformation as well as other low energy conformations were found to contain no intramolecular hydrogen bond. In fact, no hydrogen bonded conformations were found within 10 Kcal mol^{-1} of the lowest energy conformation.

In order to better correlate the configuration of the molecules with its likelihood to form intramolecular hydrogen bonds, we also carried out a systematic search of their conformational preferences of the four diastereomers that would have arisen had we started the synthesis from **3a** (Table 1). Again, computational data suggest that two of these diastereomers, with (R_P,R_C,R_P,R_C) and (R_P,R_C,R_P,S_C) configuration, are likely to form intramolecular hydrogen bonds whereas the other two with (R_P,R_C,S_P,R_C) and (R_P,R_C,S_P,S_C) configuration, are unlikely to form intramolecular hydrogen bonds. A similar trend was observed for diastereomers **7a–d** (Table 2) and **8a–d** (Table 3).

Although the computational studies appeared to confirm the evidence from NMR, we wanted to confirm the relative configuration of H-bonded and non H-bonded diastereomers beyond any doubt. So at this stage, we turned our attention to determination of the structure of molecules in solid state by crystallography.

Fortunately, we were able to obtain crystal structures of all four diastereomers **8a–d** (Fig. 1–4)[11] and confirm that their relative configurations are respectively (S_P,R_C,R_P,R_C), (S_P,R_C,R_P,S_C), (S_P,R_C,S_P,S_C) and (S_P,R_C,S_P,R_C). In the other two series, compound **6a** is an oil and compound **6c** could not be crystallised. The other two diastereomers were crystalline and we were able to obtain X-ray crystal structures for them.

From the X-ray crystal structures we observed that diastereomer **6b** has (S_P,R_C,R_P,R_C) relative configuration, while diastereomer **6d** has (S_P,R_C,S_P,R_C) relative configuration. Furthermore, the relative configuration of compounds **7a** and **7b**, the two crystalline diastereomers in the series, were confirmed as (S_P,R_C,R_P,S_C) and (S_P,R_C,R_P,R_C) respectively.

Obviously, the propensity to form hydrogen bonding in solid state is influenced by many different factors including crystal packing. Therefore, no firm conclusions can be drawn from observation of hydrogen bonding in solid state. Nevertheless, it is interesting that **7a** and **7b**, as well as **6b** and **8b** which according to NMR and computational model are expected to form intramolecular H-bonding, indeed do show evidence of it in the crystal structure. In contrast, **8c** and **8d**, as well as **6d**, do not show evidence of intramolecular H-bonding in their crystal structure. Indeed, **8a** is the only example where the expected intramolecular H-bonding is not seen in the crystal structure.

Thus we can confirm that as suggested by NMR and as predicted by computational methods, in dimeric α-hydroxy

Table 1 Computed enthalpies of formation for all diastereomers of compound **6**

Relative configuration	Lowest energy in H-bonded conformations/Kcal mol^{-1}	Lowest energy in non H-bonded conformations/Kcal mol^{-1}	Number of intramolecularly H-bonded conformations[a]
(S_P,R_C,R_P,R_C) **6a**	124.134	129.155	22
(S_P,R_C,R_P,S_C) **6b**	124.141	128.206	13
(S_P,R_C,S_P,S_C) **6c**	N/A	125.968	0
(S_P,R_C,S_P,R_C) **6d**	N/A	126.652	0
(R_P,R_C,R_P,R_C)	123.963	128.416	33
(R_P,R_C,R_P,S_C)	122.504	127.459	4
(R_P,R_C,S_P,S_C)	N/A	127.657	0
(R_P,R_C,S_P,R_C)	N/A	125.991	0

[a] From a random 1296.

Table 2 Computed enthalpies of formation for all diastereomers of compound **7**

Relative configuration	Lowest energy in H-bonded conformations/Kcal mol^{-1}	Lowest energy in non H-bonded conformations/Kcal mol^{-1}	Number of intramolecularly H-bonded conformations[a]
(S_P,R_C,R_P,R_C) **7a**	158.210	160.882	10
(S_P,R_C,R_P,S_C) **7b**	159.534	161.609	11
(S_P,R_C,S_P,S_C) **7c**	N/A	160.692	0
(S_P,R_C,S_P,R_C) **7d**	N/A	161.486	0
(R_P,R_C,R_P,R_C)	156.955	160.573	16
(R_P,R_C,R_P,S_C)	158.400	161.573	1
(R_P,R_C,S_P,S_C)	N/A	160.780	0
(R_P,R_C,S_P,R_C)	N/A	161.641	0

[a] From a random 1152.

Table 3 Computed enthalpies of formation for all diastereomers of compound **8**

Relative configuration	Lowest energy in H-bonded conformations/Kcal mol^{-1}	Lowest energy in non H-bonded conformations/Kcal mol^{-1}	Number of intramolecularly H-bonded conformations[a]
(S_P,R_C,R_P,R_C) **8a**	124.352	127.892	25
(S_P,R_C,R_P,S_C) **8b**	123.948	127.181	4
(S_P,R_C,S_P,S_C) **8c**	N/A	126.598	0
(S_P,R_C,S_P,R_C) **8d**	N/A	125.913	0
(R_P,R_C,R_P,R_C)	124.377	127.255	5
(R_P,R_C,R_P,S_C)	122.352	126.975	12
(R_P,R_C,S_P,S_C)	N/A	126.917	0
(R_P,R_C,S_P,R_C)	N/A	125.365	0

[a] From a random 1152.

phenylphosphinates, the relative configuration of carbon and phosphorus stereocenters influences the propensity of the molecules to fold over and form intramolecular hydrogen bonding.

It is clear that sequential application of Hewitt reaction followed by phospha-aldol reaction could be carried out iteratively *ad infinitum*. Therefore the method described herein is a means for synthesis of longer oligomeric chain of α-hydroxy phenylphosphinate residues. To demonstrate this, we used dimer compound **6b** to prepare, *via* intermediates **9a** and **9b**, a mixture of four diastereomeric trimers, **10a–d** (Scheme 2). Having shown that the methodology is applicable to the synthesis of oligomeric α-hydroxy phenylphosphinates, we are currently in the process of further investigation of the conformation preferences of the trimers and longer chain molecules.

In summary, we have shown a method for preparation of oligomeric α-hydroxy phenylphosphinate chains *via* sequential Hewitt and phospha-aldol reactions. Furthermore, we have shown, using nuclear magnetic resonance, computational studies and X-ray crystallography that dimeric α-hydroxy phenylphosphinates fold over to form intramolecularly hydrogen bonded structures, depending on the relative configuration of the carbon and phosphorus atoms.

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ and MeOD on Bruker AM360, AMX400, and JEOL ECA-600 operating respectively at 360, 400 and 600 MHz for ^{1}H and corresponding values for ^{13}C (90, 100, 150 MHz) and ^{31}P (145, 162, 243 MHz). Sodium chloride plates were used to run the IR spectra using either a Digilab UMA400 or a Perkin-Elmer FTIR instrument. Solids were run as a dispersion in Nujol or by grinding with potassium bromide powder, and oils were run neat as a thin film. Electrospray (ES) and Electron Impact (EI) ionisation techniques were used for mass spectrometry. Low resolution spectra were conducted on either Micromass Quattro Ultima or Jeol AX505X spectrometers. High resolution mass spectra were carried out by EPSRC Mass Spectrometry

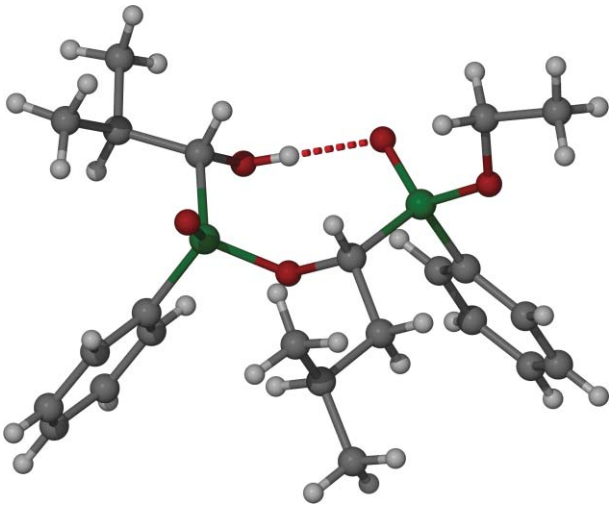


Fig. 1 X-ray crystal structure of (S_P,R_C,R_P,R_C)/(R_P,S_C,S_P,S_C) diastereomer, compound **8a**.

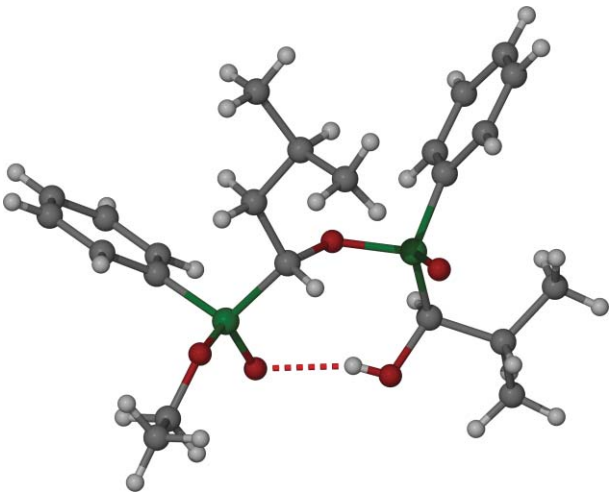


Fig. 2 X-ray crystal structure of (S_P,R_C,R_P,S_C)/(R_P,S_C,S_P,R_C) diastereomer, compound **8b**.

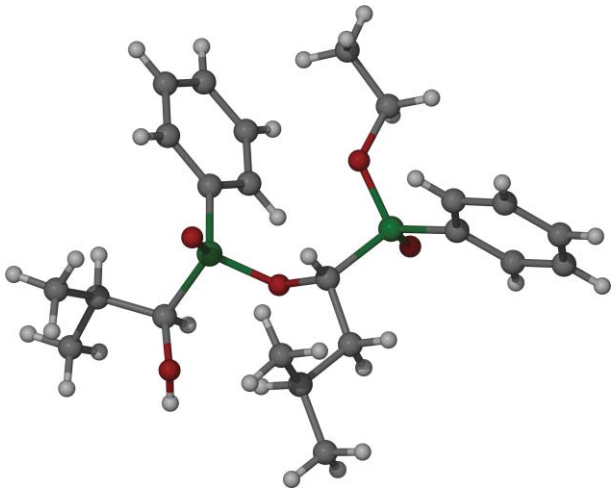


Fig. 3 X-ray crystal structure of the (S_P,R_C,S_P,S_C)/(R_P,S_C,R_P,R_C) diastereomer, compound **8c**.

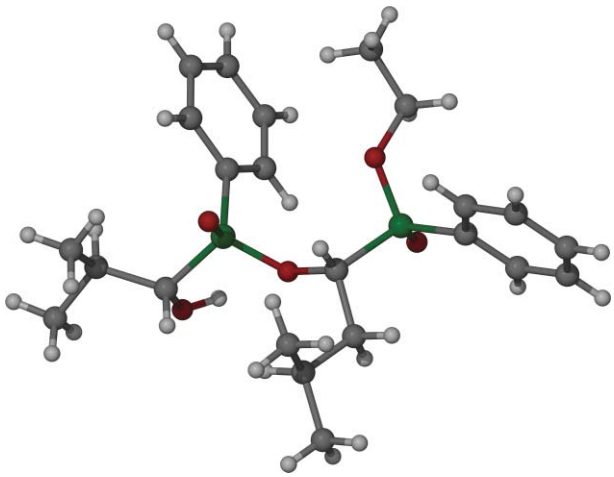


Fig. 4 X-ray crystal structure of the (S_P,R_C,S_P,R_C)/(R_P,S_C,R_P,S_C) diastereomer, compound **8d**.

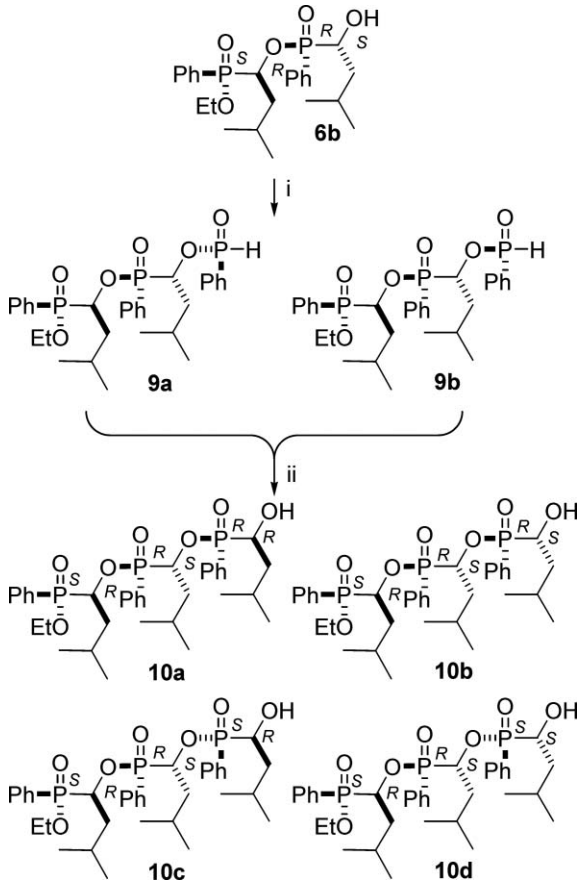
service at the University of Swansea using a Finnigan MAT 900 XLT spectrometer. Microanalyses were performed at the London Metropolitan University. Petroleum ether (petrol) used throughout is the boiling point fraction 60–80 °C.

Compound 3b

Ethyl phenylphosphonite 1 (15 g, 88 mmol) was mixed with 3-methyl-2-butenal 2 (8.5 ml, 88 mmol). KF (30 g) was added and the mixture was stirred until it was completely solid. Methylene chloride (80 ml) was added and the reaction was allowed to stir for 10 min. KF was filtered off through celite and the solvent was removed *in vacuo.* Recrystallisation using methylene chloride and pet. ether gave (*1-hydroxy-3-methylbut-2-enyl*) *phenylphosphinic acid ethyl ester* as colourless crystals (first crop 6.0 g, 27%). Mp 113–115 °C; ^{1}H NMR δ_H ($CDCl_3$) 1.35 (3H, t, J_H 7, OCH_2CH_3), 1.47 [3H, d, J_H 4, $=C(CH_3)_2$], 1.69 [3H, d, J_H 4, $=C(CH_3)_2$], 3.90–3.93 (1H, t, $J_P = J_H = 6$, OH), 4.00–4.11 (1H, m, OCH_2CH_3), 4.17–4.26 (1H, m, OCH_2CH_3), 4.73 (1H, ddd, $J_P = 10$, $J_H = 6$, $J_H = 4$, PC*H*), 5.13–5.16 (1H, m, C*H*=CMe_2), 7.44–7.58 (3H, m, Aromatic H), 7.75–7.80 (2H, m, Aromatic H); ^{31}P NMR $\delta_P\{H\}$ ($CDCl_3$) 38.77; ^{13}C NMR $\delta_C\{H\}$ ($CDCl_3$) 17.0 (d, J_P 5, CH_2CH_3), 18.9 (d, J_P 3, CH_3), 26.3 (d, J_P 3, CH_3), 62.04 (d, J_p 7, OCH_2), 68.8 (d, J_P 116, P*C*H), 120.13 (=*C*Me_2), 128.9 (d, J_p 121, Aromatic C), 128.7 (d, J_p 12, 2 × Aromatic CH), 132.8 (d, J_p 3, Aromatic CH), 133.1 (d, J_p 10, 2 × Aromatic CH), 139.1 (d, J_p 13, *C*H=CMe_2), 139.43 (=*C*Me_2). IR 3273 (OH), 1440, 1226, 1211, 1163, 1121, 1051 (P=O) cm^{-1}. *m/z* (EI) 254 (M^+, 20), 225 (10), 187 (17), 170 (100), 142 (100), 105 (19), 85 (29), 78 (53). HRMS: calculated for $C_{13}H_{19}O_3PNa$ [MNa^+] 277.0964, found 277.0968. Anal calc. for $C_{13}H_{19}O_3P$: C, 61.41; H, 7.53; found C, 61.40; H, 7.60%.

Compound 4

Compound 3b (10.28 g, 40.5 mmol) and 10% Pd/C (2 g, 20%wt) in ethyl acetate (200 ml) were hydrogenated overnight. The catalyst was filtered off using celite and the solvent was removed *in vacuo* to give (*1-hydroxy-3-methyl butyl*) *phenyl phosphinic acid ethyl ester* as a solid (10.36 g, quantitative yield). Mp 96–98 °C; ^{1}H NMR δ_H ($CDCl_3$) 0.88 [3H, d, $CH(CH_3)_2$], 0.93 [3H, d, $CH(CH_3)_2$], 1.35 (3H, t, J_H 7, OCH_2CH_3), 1.40–1.45 and 1.44–1.60



Scheme 2 (i) Pyridine, $(COCl_2)_3$, CH_2Cl_2, 0 °C then $PhP(OH)_2$, reflux; (ii) Et_3N, TMSCl, CH_2Cl_2, 0 °C, then ^{i}BuCHO.

(2H, 2 × m, CH_2^{i}Pr), 1.85–1.93 (1H, m, CHMe$_2$), 2.49 (1H, m, OH), 3.98–4.08 (2H, m, PCHCH$_2$ and OCH_2), 4.08–4.26 (1H, m, OCH_2CH$_3$), 7.43–7.73 (3H, m, Aromatic H), 7.75–7.85 (2H, m, Aromatic H); ^{31}P NMR $\delta_P\{H\}$ ($CDCl_3$) 40.49; ^{13}C NMR $\delta_C\{H\}$ ($CDCl_3$) 15.6 (d, J_P 5, CH_3), 20.0 (CH_3), 22.53 (CH_3), 22.1 (*C*HMe$_2$), 38.4 (CH_2), 60.4 (d, J_P 7, OCH_2), 67.3 (d, J_P 114, CH), 127.3 (d, J_P 119, Aromatic C), 127.5 (d, J_P 12, 2 × Aromatic CH), 131.6 (d, J_P 9, 2 × Aromatic CH), 132.8 (d, J_p 3, Aromatic CH); IR 3259 (OH), 3062-2869 (CH), 1592, 1469, 1439, 1389, 1210 (P=O) cm^{-1}. HRMS: calculated for $C_{13}H_{21}O_3PNa$ [MNa$^+$] 279.1121, found 279.1125. *m/z* (EI) 257 (MH$^+$, 22), 241 (9), 197 (16), 184 (25), 170 (100), 156 (22), 141 (100), 125 (14), 105 (41), 77 (65), 51 (13). Anal calc. for $C_{13}H_{21}O_3P$: C, 60.93, H, 8.26; found C, 60.98, H, 8.10%.

Compound 5a/b

Triphosgene (3.47 g, 12 mmol), followed by pyridine (2.85 ml, 35 mmol) were added to a stirred solution of 4 (9.00 g, 35 mmol) in methylene chloride (150 ml) maintained at 0 °C and under a dry nitrogen atmosphere. The mixture was left stirring for 3 h at 0 °C. Phenylphosphinic acid (5.63 g, 40 mmol) followed by pyridine (3.21 ml, 40 mmol) were carefully added to the stirred solution of the so formed chloroformate. (*Caution! Exothermic reaction*; *rapid effervescence*). Once the effervescence had stopped the stirred solution was left to warm up to room temperature under a dry nitrogen atmosphere and then set to reflux for 2 h. After cooling, the solution was poured into 0.1 M hydrochloric acid (50 ml) and the organic layer was separated. The organic extracts were washed with water (50 ml) and dried using Na_2SO_4. The combined organic extracts were stripped of solvent *in vacuo* to give crude ethyl 3-methyl-1-phenylphosphinoylbutyl(phenyl)phosphinate as a colourless oil (14 g). ^{1}H NMR δ_H ($CDCl_3$) 0.75 (3H, d, J_P 6, 2 × Me), 0.82 (3H, d, J_P 6, 2 × Me), 1.37 (3H, t, J_P 7, OCH_2CH_3), 1.35–1.77 (3H, m, CHMe$_2$ and CH_2^{i}Pr), 3.57–3.90 (2H, m, OCH_2CH_3), 4.80–4.9 (1H, m, PCH), 7.41 (1H, d, J_P 640, PH), 7.35–7.76 (10H, m, Aromatic H); ^{31}P NMR $\delta_P\{H\}$ ($CDCl_3$) 28.2 (d, J_P 12), 36.6 (d, J_P 12); ^{13}C NMR $\delta_C\{H\}$ ($CDCl_3$) 16.1 (d, J_P 5, CH_3), 20.5 (CH_3), 23.1 (CH_3), 23.5 (*C*HMe$_2$), 39.0 (CH_2), 61.4 (d, J_P 7, OCH_2), 65.0 (d, J_P 117, CH), 127.3-132.6 (Aromatic C and CH); IR 3400 (OH), 2840–2951 (CH), 1448, 1405, 1113 (P=O), 1017 (P=O) cm^{-1}. *m/z* (EI): 403.1 MNa$^+$. HRMS: calculated for $C_{19}H_{26}O_4P_2Na$ [MNa$^+$]: 403.1204, found: 403.1220.

Addition of 5a/b to isovaleraldehyde

Triethylamine (10 ml, 72 mmol) was added to a stirred solution of crude compound **5ab** (14 g) in methylene chloride (150 ml) maintained at 0 °C under a dry nitrogen atmosphere. After 15 min TMSCl (9.1 ml, 72 mmol) was slowly added (*Caution! Excessive fuming*) and the reaction mixture was left stirring for a further 15 min. Isovaleraldehyde (4.25 ml, 40 mmol) was added and the stirred reaction mixture was left to warm up to room temperature overnight under a dry nitrogen atmosphere. A sample of the crude reaction mixture was withdrawn and NMR analysis demonstrated that the reaction had gone to completion. The reaction mixture was poured into water (50 ml) and the organic layer was separated. The aqueous phase was washed with methylene chloride (2 × 25 ml). The combined organic extracts were dried over Na_2SO_4 and stripped of solvent *in vacuo*. Tetrabutylammonium fluoride (20 ml of a 1M solution in THF) was added to a stirred solution of this crude product in THF (20 ml). After 5 min, the reaction mixture was poured into water (60 ml) and was extracted with methylene chloride (3 × 60 ml). The combined organic extracts were dried over Na_2SO_4 and stripped of solvent *in vacuo*. The residue was subjected to chromatography (EtOAc–pet. ether 2 : 1, then 1 : 1, then neat EtOAc) the appropriate fractions were combined, stripped of solvent and crystallised, if appropriate, to afford:

Compound 6a colourless oil, (R_f(tlc) = 0.7 in ether), 3 g (18% over three steps). ^{1}H NMR δ_H ($CDCl_3$) 0.65 (3H, d, J_H 7, Me), 0.70 (3H, d, J_H 7, Me), 0.75 (3H, d, J_H 7, Me), 0.80 (3H, d, J_H 7, Me), 1.17–1.27 (2H, m, CH_2^{i}Pr), 1.34 (3H, t, J_H 7, OCH_2CH_3), 1.70–1.79 (1H, m, CHMe$_2$), 1.84–1.94 (1H, m, CHMe$_2$), 4.05–4.20 (2H, q, J_H 7, OCH_2CH_3), 4.29–4.38 (1H, ddd, J_H 2.6, J_H 4.2, J_H 10.4, J_p 22.2, PCH_b), 4.97 (1H, ddd, J_H 2.8, J_H 10.4, J_p 22.2, PCH_a), 6.16 (1H, dt, J_H 4.2, J_p 1.5, OH), 7.42–7.52 (4H, m, Aromatic H), 7.57–7.63 (2H, m, Aromatic H), 7.72–7.77 (2H, m, Aromatic H), 7.98–8.03 (2H, m, Aromatic H);^{31}P NMR $\delta_P\{H\}$ ($CDCl_3$) 40.25 (d, J_P 14), 46.05 (d, J_P 14); ^{13}C NMR δ_C {H} ($CDCl_3$) 17.3 (CH_3), 21.82 (CH_3), 21.88 (CH_3), 23.84 (CH_3), 24.36 (CH_3), 25.5 (CH), 25.8 (CH), 40.8 (CH_2), 41.71 (CH_2), 64.3 (CH_2), 73 (d, J_p 112, CH), 73 (d, J_p 117 CH), 126.1 (d, J_p 127, aromatic C), 127.9 (d, J_p 126, aromatic C), 128.1 (d, J_p 12.2, 2 : aromatic CH), 128.8 (d, J_p 12.6, 2 : aromatic CH), 132.2 (d, J_p 8.3, 2 : aromatic CH), 132.3 (d, J_p 2.6, aromatic CH), 132.8 (d, J_p 9.6, 2 × aromatic CH), 133.3 (d, J_p 2.7, aromatic CH). IR 3294 OH, 2869, 2957 (CH), 1592, 1468,

1439, 1387, 1368, 1300, 1249, 1218, 1122 (P=O) cm^{-1}. HRMS: calculated for $C_{24}H_{36}O_5P_2Na$ [MNa^+] 489.1936, found 489.1923. *m/z* (ES) 467.3 [MH^+]. Anal calc. for $C_{24}H_{36}O_5P_2$: C, 61.79, H, 7.78; found C, 61.89, H, 7.67%.

Compound 6b colourless crystals, (R_f(tlc) = 0.4 in ether), 3 g (18% over three steps). Mp 90–95 °C. ^{1}H NMR δ_H ($CDCl_3$) 0.65 (3H, d, J_H 7, Me), 0.74 (3H, d, J_H 7, Me), 0.83 (3H, d, J_H 7, Me), 0.86 (3H, d, J_H 7, Me), 1.16–1.34 and 1.76–1.86 (3H and 1H, m, 2 × CH_2^{i}Pr),1.34 (3H, t, J_H 7, OCH_2CH_3), 1.52–1.64 (1H, m, $CHMe_2$), 1.86–1.94 (1H, m, $CHMe_2$), 4.00–4.19 (3H, m, OCH_2CH_3 and PCH_b), 5.15 (1H, ddd, J_H 2.9, J_H 11.3, J_p 21.6, PCH_a), 5.92 (1H, dd, J_H 5.8 J_P 1, OH), 7.31–7.80 (10H, m, Aromatic H). ^{31}P NMR δ_P\{H\} ($CDCl_3$) 41.0 (d, J_P 14), 42.1 (d, J_P 14). ^{13}C NMR δ_C\{H\} ($CDCl_3$) 16.6 (d, J_p 6 CH_3), 20.9 (CH_3), 21.1 (CH_3), 23.4 (CH_3), 23.6 (CH_3), 23.7 (d, J_p 11, CH), 24.2 (d, J_p 12, CH), 38.8 (d, J_p 3 CH_2^{i}Pr), 41.1 (d, J_p 2 CH_2^{i}Pr), 62.4 (d, J_p 7 OCH_2), 69.3 (d, J_p 105 CH), 71.3 (dd, J_p 112 J_p 8 CH), 127.0 (d, J_p 128, aromatic C), 128.9 (d, J_p 128, aromatic C), 128.4 (d, J_p 12.2, 2 × aromatic CH), 128.7 (d, J_p 12.6, 2 × aromatic CH), 131.2 (d, J_p 9.2, 2 × aromatic CH), 132.3 (d, J_p 2.3, aromatic CH), 132.6 (d, J_p 11.6, 2 × aromatic CH), 133.2 (d, J_p 2.5, aromatic CH). IR 3284 OH, 2720–3053 CH, 1589, 1466, 1441, 1414, 1388, 1377, 1366, 1340, 1306, 1230, 1194, 1161, 1121 (P=O), 1077, 1034 cm^{-1}. *m/z* (EI): 467.2 MH^+, 489.2 MNa^+. HRMS: calculated for $C_{24}H_{36}O_5P_2Na$ [MNa^+] 489.1936, found 489.1921. Anal calc. for $C_{24}H_{36}O_5P_2$: C, 61.79, H, 7.78; found C, 61.84, H, 7.68%.

Compound 6c white amorphous solid (R_f(tlc) = 0.25 in ether) 2.5 g (15% over three steps). Mp 120–125 °C. ^{1}H NMR δ_H ($CDCl_3$) 0.51 (3H, d, J_H 7, Me), 0.74 (3H, d, J_H 7, Me), 0.92 (6H, d, J_H 7, Me), 0.94 (3H, d, J_H 7, Me), 1.18 (3H, t, J_H 7, OCH_2CH_3), 1.20–1.95 (6H, m, 2 × $CHMe_2$ and CH_2^{i}Pr), 3.95 (2H, quint, J_H 7, J_P 7, OCH_2CH_3), 4.24 (1H, m, PCH_b), 4.35 (1H, bs, OH), 4.55 (1H, ddd, J_H 3.6, J_H 9.7, J_p 17.8, PCH_a), 7.48–7.52 (4H, m, Aromatic H), 7.57–7.63 (2H, m, Aromatic H), 7.77–7.78 (2H, m, Aromatic H), 7.99–8.06 (2H, m, Aromatic H). ^{31}P NMR δ_P\{H\} ($CDCl_3$) 38.8 (d, J_P 14), 41.8 (d, J_P 14).^{13}C NMR δ_C\{H\} ($CDCl_3$) 16.3 (d, J_p 6 CH_3), 20.9 (CH_3), 21.2 (CH_3), 23.1 (CH_3), 23.5 (CH_3), 23.7 (d, J_p 11, CH), 24.3 (d, J_p 14, CH), 38.90 (d, J_p 3 CH_2^{i}Pr), 40.17 (CH_2^{i}Pr), 61.8 (d, J_p 7 OCH_2), 70.0 (d, J_p 115 CH), 72.7 (dd, J_P 121 J_P 11 CH) 126.7 (d, J_p 112, aromatic C), 127.1 (d, J_p 126, aromatic C), 128.4 (d, J_p 12.2, 2 × aromatic CH), 128.7 (d, J_p 12.6, 2 × aromatic CH), 132.6 (d, J_p 9.4, 2 × aromatic CH), 132.7 (d, J_p 2.3, aromatic CH), 133.1 (d, J_p 9.2, 2 × aromatic CH), 133.1 (d, J_p 2.2, aromatic CH). IR 3280 OH, 2853, 2924 (CH), 1591, 1461, 1443, 1377, 1234, 1182, 1121 P=O, 1073 cm^{-1}. *m/z* (EI): 467.2 MH^+, 489.2 MNa^+. HRMS: calculated for $C_{24}H_{36}O_5P_2Na$ [MNa^+] 489.1936, found 489.1920.

Compound 6d colourless crystals (R_f(tlc) = 0.24 in ether) 0.2 g (1%). Mp 101–107 °C ^{1}H NMR δ_H ($CDCl_3$) 0.55 (3H, d, J_H 7, Me), 0.75 (3H, d, J_H 7, Me), 0.92 (6H, d, J_H 7, Me), 0.92 (3H, d, J_H 7, Me), 1.12 (3H, t, J_H 7, OCH_2CH_3), 1.30–2.0 (6H, m, 2 × $CHMe_2$ and CH_2^{i}Pr), 3.9 (2H, quint, J_H 7, J_P 7, OCH_2CH_3), 4.1 (1H, m, PCH_b), 4.2 (1H, bs, OH), 4.62 (1H, ddd, J_H 3.6, J_H 9.8, J_p 17, PCH_a), 7.46–7.49 (4H, m, Aromatic H), 7.55-7.59 (2H, m, Aromatic H), 7.72–7.75 (2H, m, Aromatic H), 7.99–8.04 (2H, m, Aromatic H). ^{31}P NMR δ_P\{H\} ($CDCl_3$) 38.2 (d, J_P 14), 41 (d, J_P 14).^{13}C NMR δ_C\{H\} ($CDCl_3$) 16.2 (d, J_p 5.8 CH_3), 20.9 (CH_3), 21 (CH_3), 23.2 (CH_3), 23.7 (CH_3), 23.8 (d, J_p 11, CH), 24.3 (d, J_p 13, CH), 39.25 (CH_2^{i}Pr), 40.12 (CH_2^{i}Pr), 61.75 (d, J_p 6.5 OCH_2), 69.55 (d, J_p 112 CH), 72.6 (dd, J_P 122 J_P 11 CH) 127.2 (d, J_p 98, aromatic C), 127.9 (d, J_p 86, aromatic C), 128.5 (d, J_p 12.3, 2 × aromatic CH), 128.8 (d, J_p 13, 2 × aromatic CH), 132.7 (d, J_p 2.3, aromatic CH), 132.78 (d, J_p 9.4, 2 × aromatic CH), 133.1 (d, J_p 9.4, 2 × aromatic CH), 133.21 (d, J_p 2.2, aromatic CH). IR 3300 OH, 2868, 2957 CH, 1591, 1468, 1439, 1387, 1304, 1221, 1119 (P=O), 1070, 1025 cm^{-1}. *m/z* (EI): 467.2 MH^+, 489.2 MNa^+. HRMS: calculated for $C_{24}H_{36}O_5P_2Na$ [MNa^+] 489.1936, found 489.1927.

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11 *Crystal data for compound* ***8a*** $C_{23}H_{34}O_5P_2$, $M = 452.44$, colourless plate, triclinic, space group $P\bar{1}$ (No. 2), $a = 9.1386(2)$, $b = 11.9523(2)$, $c = 12.7388(3)$ Å, $\alpha = 113.9030(10)$, $\beta = 96.4940(10)$, $\gamma = 91.6580(10)°$, $V = 1259.64(5)$ Å^3, $Z = 2$, $D_c = 1.193$ g/cm^3, $F_{000} = 484$, Bruker APEX-II CCD, MoKα radiation, $\lambda = 0.71073$ Å, $T = 296(2)$K, $2\theta_{max} = 59.9°$, 88980 reflections collected, 7245 unique ($R_{int} = 0.0336$). Final *GooF* = 1.047, $R1 = 0.0404$, w$R2 = 0.1037$, *R* indices based on 5180 reflections with $I > 2\sigma(I)$ (refinement on F^2), 280 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.201$ mm^{-1}. *Crystal data for compound* ***8b***: $C_{23}H_{34}O_5P_2$, $M = 452.44$, triclinic, $a = 8.6935(7)$ Å, $b = 23.972(2)$ Å, $c = 24.195(2)$ Å, $\alpha = 73.726(5)°$, $\beta = 88.844(5)°$, $\gamma = 88.865(5)°$, $V = 4838.6(7)$ Å^3, $T = 173(2)$ K, space group $P\bar{1}$, $Z = 8$, 249 416 reflections measured, 17 037 independent reflections ($R_{int} = 0.2501$). The final R_1 values were 0.0698 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1404 ($I > 2\sigma(I)$). The final R_1 values were 0.1964 (all data). The final w$R(F^2)$ values were 0.1694 (all data). *Crystal data for compound* ***8c/d*** $C_{23}H_{34}O_5P_2$, $M = 452.44$, colourless needle, trigonal, space group $R\bar{3}$ (No. 148), $a = b = 20.3573(4)$, $c = 31.9361(12)$ Å, $V = 11461.8(5)$ Å^3, $Z = 18$, $D_c = 1.180$ g cm^{-3}, $F_{000} = 4356$, MoKα radiation, $\lambda = 0.71073$ Å, $T = 120(2)$K, $2\theta_{max} = 55.0°$, 40 132 reflections collected, 5866 unique ($R_{int} = 0.0444$). Final GooF = 1.046, $R1 = 0.0455$, w$R2 = 0.1010$, *R* indices based on 4616 reflections with $I > 2\sigma(I)$ (refinement on F^2), 326 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.199$ mm^{-1}.

