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Synthesis of a novel diarylphosphinic acid: a distorted ground state mimic and transition state analogue for amide hydrolysis

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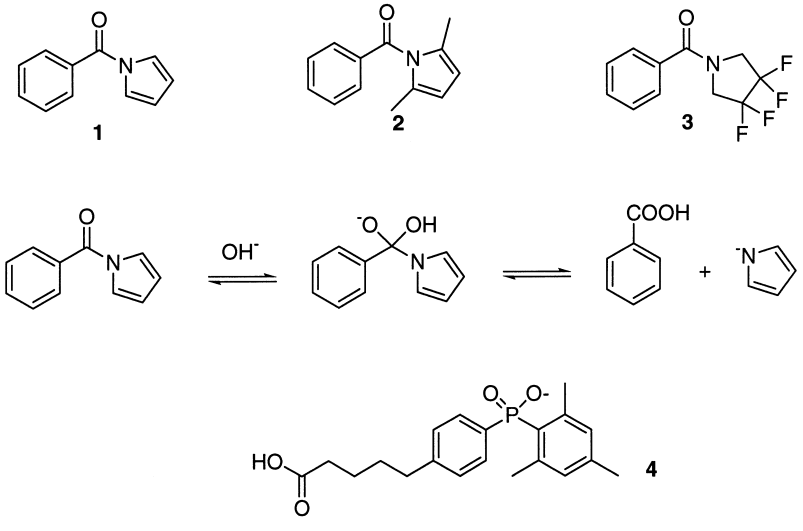
Abstract—We describe herein the synthesis of a new unsymmetrical diarylphosphinic acid, a hapten aimed to produce catalytic antibodies for the hydrolysis of heterocyclic amides. The phosphinate functionality was selected as a mimic both of the tetrahedral intermediate and the transition state of higher energy along the reaction profile. The phenyl and 2,4,6-(trimethyl)-phenyl groups flanking the phosphinate were chosen in order to impose rotation around the P–C bond, a choice supported by ab initio calculations. This new hapten should elicit catalytic antibodies whose binding site could affect the distortion at nitrogen as well as the twist along the N–C(O) bond for heterocyclic amides. This hapten along with a series of new sterically hindered unsymmetrical phosphinic acid derivatives was prepared by a key palladium-catalysed step.

1. Introduction

The generation of amidase-like antibodies has been and is still an extremely challenging task that bears high therapeutical potential.[1] A few studies have shown promising results, but this area of research still remains a testing ground for new hapten strategies.[2] This work is directed towards the generation of amidase antibodies and is focused on eliciting antibodies against haptens mimicking both a distorted ground state and a transition state.[3] This strategy was previously explored by Hansen et al. as a new approach to sequence-specific protease antibodies.[4] Haptens such as 2-*cis*-amino-3-*cis*-hydroxycyclobutane carboxylic acid and *endo*-(3-amino-2-hydroxy)bicyclo-[2.2.1]-heptane-7-*anti*-carboxylic acid in which the targeted glycyl–glycyl peptide bond was replaced by a ring-strained or torsionally-strained



Scheme 1. Design of hapten **4** for the hydrolysis of compounds **1-3**.

Keywords: antibodies; phosphinic acids and derivatives; palladium; coupling reactions.
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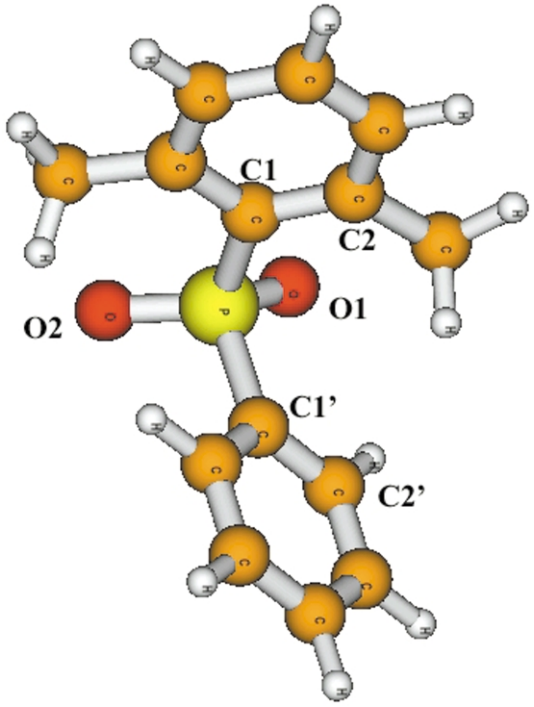


Figure 1. Preferential conformation of (2,6-dimethylphenyl)phenyl phosphinic acid.

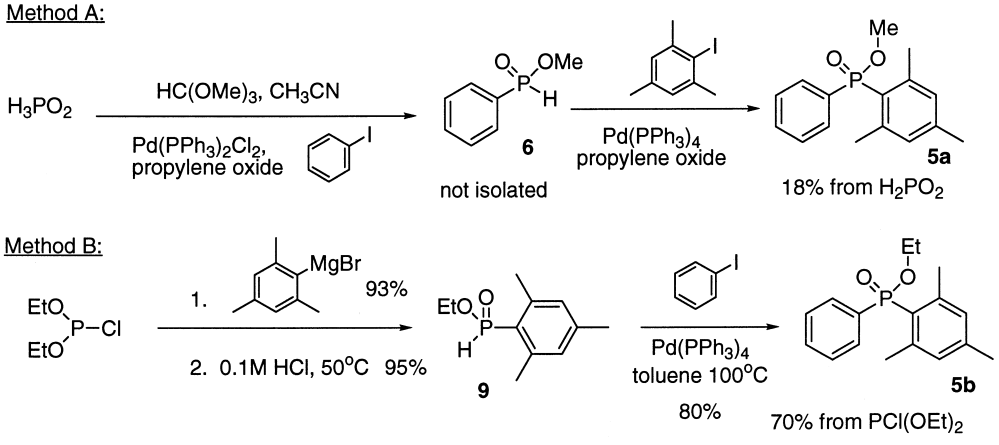
moiety were made. In pursuit of sequence-specific antibody proteases, these entities were flanked by additional amino acid residues. Also, a series of β-lactam-containing dipeptide analogues mimicking only a ring-strained ground state was prepared.[4,5] The same group of workers also synthesised 7-*trans*-amino-6-*trans*-hydroxy-spiro-[4.4]-nonanecarboxylic acid, a dipeptide analogue mimicking both torsionally-strained glycyl-proline and glycyl-glycine.[6] To our knowledge, no catalytic antibodies raised against these molecules have been reported.

Uncatalysed peptide bond hydrolysis is extremely slow at physiological pH and temperature ($t_{1/2}$ approximately 9 years).[7] In contrast to peptide bond hydrolysis, the hydrolytic cleavage of *N*-acylpyrrole, *N*-acylimidazole and some activated *N*-acylpyrrolidine derivatives is a much faster process.[8] Consequently, antibodies for the catalysis of the hydrolysis of such substrates would need to exhibit lower rate accelerations for detectable hydrolysis. We therefore chose the hydrolysis of the heterocyclic amides **1**–**3**, which contain amine portions of reduced basicity, as model reactions to test a novel hapten that can mimic both the transition state and a distorted ground state. We report herein the design and the synthesis of a new hapten **4** aimed to elicit amidase antibodies for the hydrolysis of the heterocyclic amides **1**–**3** (Scheme 1). The conformation of a close model of compound **4** was determined by ab initio calculations.

2. Results and discussion

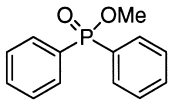
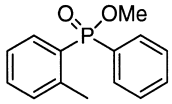
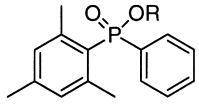
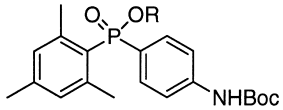
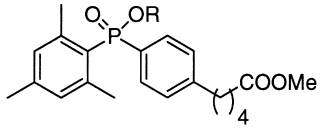
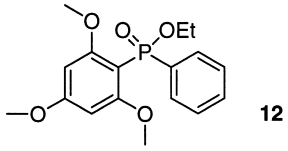
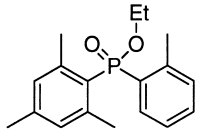
2.1. Hapten design

It was shown that the base catalysed hydrolysis of aroyl pyrrole derivatives proceeds via rate determining decomposition of the tetrahedral intermediate from which the leaving group departs as an anion.[9] This step could be spontaneous or catalysed by $^{-}$OH and calculations suggested that the transition state for the spontaneous decomposition of the intermediate is similar to the tetrahedral intermediate itself.[10] The unsymmetrical diarylphosphinic acid derivative **4** (Scheme 1) was therefore selected based on the following criteria. We selected the phosphinate functionality as a mimic both of the tetrahedral intermediate and of the transition state, a choice supported by the recent computational and ab initio analysis reported by Tantillo and Houk.[11] It is interesting to note that, in contrast to phosphonate and phosphonamidate functions,[1,12] the phosphinate group has not often been selected as a transition state analogue for hydrolytic reaction. However, Benkovic and coworkers described the successful use of a cyclic phosphinate in the generation of catalytic antibodies for the deamidation of a model dipeptide through an intermediate succinimide.[13] The phosphinate functionality in compound **4** was flanked by two phenyl groups, one of them being substituted on positions 2, 4 and 6 by methyl groups. It is anticipated that the presence of the *ortho* methyls at position 2 and 6 will impose rotation around the P–C bond. To determine the conformation of the phosphinate compound **4** (Scheme 1), calculations were performed for a diarylphosphinate in which one of the phenyl groups presents no substituents



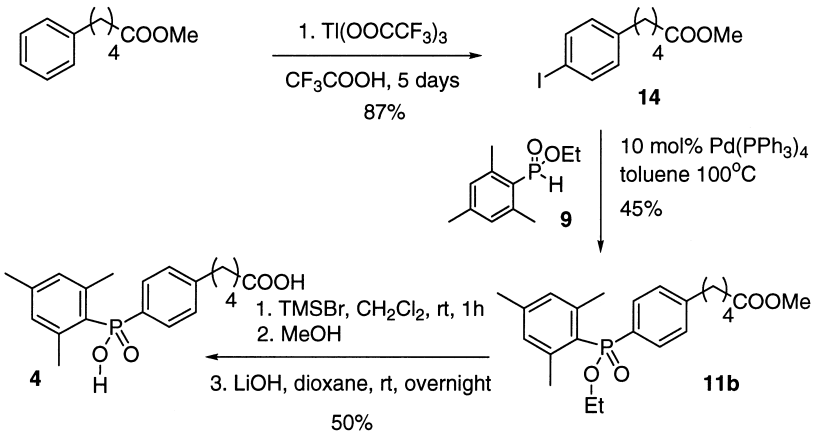
Scheme 2. Synthetic approaches to the synthesis of unsymmetrical diarylphosphinic acid derivatives **5a** and **5b**.

Table 1. Synthesis of a series of unsymmetrical diarylphosphinic acid derivatives

Entry	Products	Method	Yield[a,b] (%)
1	 **7**	A	64
2	 **8**	A	49
3	 R=Me **5a** R=Et **5b**	A B	**5a** 18 **5b** 80, 92[c], 62[d]
4	 R=Me **10a** R=Et **10b**	A B	**10a** 18 **10b** 38[e]
5	 R=Me **11a** R=Et **11b**	A B	**11a** 20 **11b** 45[f], 48[c]
6	 **12**	B	74
7	 **13**	B	33, 55[d]

[a] Isolated yields after silica gel chromatography.
[b] Yield for the Pd cross-coupling step.
[c] Pd $(OAc)_2$ (3 mol%) combined with 13 mol% dppf was used instead of $Pd(PPh_3)_4$.
[d] K_3PO_4 (1.5 mol%) was added to $Pd(PPh_3)_4$ as an additive.
[e] $Pd_2(dba)_3$ (5 mol%) was used instead of $Pd(PPh_3)_4$.
[f] Compound **5b** (25%) was isolated as a side product.

and the other shows methyl substituents at the 2 and 6 positions (Fig. 1). The B3LYP function[14] with a 6-31+G* basis set was used to describe the electronic structure of the molecule. All calculations were done with the Jaguar program.[15] The optimised geometry is shown in Fig. 1. The most important result concerns the orientation of the two phenyl groups. For the 2,6-(dimethyl)-phenyl group, the O2–P–C1–C2 dihedral angle is 1.8°, O1–P–C1–C2 angle is −42.8° and C2–C1–P–C1′ is 70.0°. For the unsubstituted phenyl group, we get values of −50.7° for O2–P–C1′–C2′, −5.3° for O2–P–C1′–C2′ and −118.9° for C2′–C1′–P–C1 dihedral. Thus the 2,6-(dimethyl)-phenyl group is oriented to be almost coplanar with the O2–P–C1 plane, whereas the unsubstituted phenyl group is almost coplanar with the O1–P–C1′ plane. A more detailed description of these calculations including solvent effects will be the subject of



Scheme 3. Synthesis of hapten **4**.

a future publication. With these results in hand, it seems to us that hapten **4** should elicit catalytic antibodies whose binding site could affect distorsion at nitrogen as well as the twist along the N–C(O) bond for substrates **1**–**3**. The hapten **4** could therefore be regarded both as a distorted ground state mimic of compounds **1**–**3** and a transition state analogue for their hydrolysis.

2.2. Synthesis

In the retrosynthetic analysis of compound **4**, the diarylphosphinate would derive from a palladium-catalysed key step. Several reports have described the synthesis of unsymmetrical diarylphosphinic acid derivatives[16] but, to our knowledge, the preparation of unsymmetrical diarylphosphinic acid derivatives for which one of the phenyl groups is substituted on both *ortho*-positions has not been reported. In a preliminary experiment, we first applied the strategy developed by Schwabacher et al.[16a] to the synthesis of the model compound **5a** (Scheme 2, Method A and Table 1, entry 3). The procedure relies on a sequential palladium-catalysed cross-coupling of the two different aryl iodides with methylphosphinate. In a typical procedure, a solution of methylphosphinate prepared in situ by the reaction of anhydrous phosphinic acid with an excess of trimethyl orthoformate was treated with iodobenzene in acetonitrile in the presence of excess propylene oxide (as HI scavenger) and a catalytic amount of $Pd(PPh_3)_2Cl_2$. One hour reflux at 75°C provided phenylphosphinic acid methyl ester **6** which was not purified but was freed of the excess of methyl phosphinate and other side products by treatment with $NaHCO_3$. Subjection of this material to iodomesitylene under palladium catalysis in the presence of propylene oxide led to the formation of the expected product **5a** albeit in only 18% yield. When the above sequence of reactions was reversed, coupling first the more sterically hindered iodomesitylene followed by iodobenzene, no improvements were observed. Subsequently, in a series of control experiments using the same procedure, we prepared compounds **7** and **8** in 64 and 49% chemical yield, respectively (entries 1 and 2, Table 1). These results suggest that under these conditions the palladium-catalysed cross-coupling is sensitive to steric effects as reflected by the decrease in the chemical yields as the second aryl iodide is more heavily substituted. In addition, it is likely that the methylphosphinate or the first intermediate might decompose at the temperature required for the palladium cross-coupling process.[17] After several unsuccessful attempts to optimise this reaction, we concentrated our efforts on the preparation of compound **5b** having an ethyl instead of the more sensitive methyl phosphinate functionality. Compound **5b** was successfully prepared in three steps according to the methodology of Xu16b,c (Scheme 2, Method B and Table 1, entry 3). Diethylmesitylenephosphonite was first prepared in 93% yield by the reaction of mesitylenemagnesium bromide with diethyl phosphorochloridite in refluxing THF. It was subsequently smoothly converted into the corresponding key intermediate **9** in 95% yield by treatment with 0.1 M hydrochloric acid at 50°C. Interestingly, the palladium-catalysed coupling of compound **9** with iodobenzene furnished compound **5b** in 80% yield after 2 h at 100°C in toluene. Under these conditions, it seems that the coupling occurs faster than the decomposition of the phosphinate **9**. Using Xu's methodology, compound **5b** could thus be prepared with an overall yield of 70% from the commmercially available diethyl phosphorochloridite. The same methodology was successfully applied to the synthesis of compounds **10**–**12** including functional groups, however at the expense of reduced yields (Table 1, entries 4–6). For compound **11b**, a side-product was isolated in 25% yield and identified as compound **5b**. Presumably, the unsubstituted phenyl group is derived from triphenylphosphine. Such exchange of aryl groups on Pd with those of a phosphine ligand is known.[18] The use of $Pd_2(dba)_3$ instead of $Pd(PPh_3)_4$ for the coupling process prevented the formation of the side-product but did not allow us to obtain better yields except for the preparation of compound **10b** (Table 1, entry 4). Compound **13**, exemplifying a more sterically demanding system, was prepared in 33% yield supporting the hypothesis that this methodology is also sensitive to steric effects but to a lesser extent than the methodology developed by Schwabacher. In order to maximise the yield of **13**, the addition of K_3PO_4 proved to be beneficial, however this modification is not of general scope (Table 1, entries 3 and 7).

Application of the methodology of Xu to the synthesis of compound **4** was straighforward as detailed in Scheme 3. Compound **14** was first prepared in 87% yield from methyl 5-phenylvalerate using thallium trifluoroacetate followed by sodium iodide.[19] The key palladium-catalysed coupling

proceeded smoothly in the presence of 10 mol% $Pd(PPh_3)_4$ in 45% yield. Deprotection of both the ethyl phosphinate ester and the methyl carboxylate ester using TMSBr followed by LiOH yielded compound **4** as a white solid.

3. Conclusion

The design and the synthesis of a new transition state analogue aimed at eliciting catalytic antibodies for the hydrolysis of heterocyclic amides has been reported. An efficient synthesis using a palladium cross-coupling reaction as the key step has been developed for compound **4**. The methodology used for the synthesis of compound **4** has been applied to a series of sterically hindered unsymmetrical diarylphosphinic acid derivatives thereby demonstrating the scope and limitations of this palladium coupling process. The production of monoclonal antibodies and their characterisation for catalysis will be described separately.

4. Experimental

4.1. General aspects

All reactions were performed in flame-dried glassware in an atmosphere of argon unless noted otherwise. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 and Bruker AM-500 spectrometers. ^{31}P NMR spectra were recorded on a Bruker AM-500 spectrometer at 202 MHz and were referenced externally to phosphoric acid. Infrared spectra were recorded using a Perkin–Elmer Paragon 1000 FT-IR spectrometer. Mass spectra (*m/z*) were recorded on a Micromass Platform-I APCI spectrometer. HRMS were performed on a Micromass Autospec 5000 OATof. Thin layer chromatography was performed using Merck aluminium foil backed sheets precoated with Kieselgel 60 F_{254}. Plates were visualised using UV light or $KMnO_4$. Column chromatography was performed using Sorbsil™ C_{60} H(40–60) silica gel.

4.1.1. Phenyl-(2,4,6-trimethylphenyl)-phosphinic acid methyl ester (5a). Method A. Anhydrous H_3PO_2 (455 mg, 6.9 mmol) was allowed to react with 5 equiv. of trimethyl orthoformate (3.8 ml, 34.5 mmol) for 1 h at rt. This mixture was added to a solution of iodobenzene (260 μl, 2.3 mmol), $Pd(PPh_3)_2Cl_2$ (80 mg, 0.11 mmol) and propylene oxide (1.6 ml, 23 mmol) in CH_3CN at 50°C. The reaction mixture was stirred for 6 h at reflux. After cooling to rt, the reaction mixture was diluted with EtOAc (100 ml) and washed with sat. $NaHCO_3$ (5×5 ml), H_2O (50 ml) and brine (50 ml). The organic layers were dried over $MgSO_4$ and the solvents evaporated. The crude product was dissolved in CH_3CN (18 ml) and added to a solution of $Pd(PPh_3)_4$ (prepared in situ by adding $NaBH_4$ (8 mg, 0.2 mmol) to a solution of $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol) and PPh_3 (105 mg, 0.4 mmol) in CH_3CN (10 ml)), propylene oxide (1.8 ml, 26 mmol) and 2-iodomesitylene (490 mg, 2.0 mmol). The mixture was heated at reflux for 28 h. Cooling to rt, evaporation in vacuo and purification by silica gel chromatography (EtOAc/hexane: 7/3) gave **5a** (97 mg, 18%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$): δ=2.29 (s, 3H), 2.49 (s, 6H), 3.73 (d, $^3J_{H-P}$=11.20 Hz, 3H), 6.90 (d, $^4J_{H-P}$=4.00 Hz, 2H), 7.37–7.42 (m, 2H), 7.44–7.49 (m, 1H), 7.64–7.67 (dm, $^3J_{H-P}$=6.00 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=21.07, 23.33 (d, $^3J_{CP}$=3.12 Hz), 50.55 (d, $^2J_{CP}$=6.04 Hz), 123.28 (d, $^1J_{CP}$=130.61 Hz), 128.39 (d, $^3J_{CP}$=13.08 Hz), 130.42 (d, $^2J_{CP}$=11.27 Hz), 130.78 (d, $^3J_{CP}$=13.68 Hz), 131.64 (d, $^4J_{CP}$=2.31 Hz), 133.93 (d, $^1J_{CP}$=136.04 Hz), 142.11 (d, $^4J_{CP}$=2.72 Hz), 143.85 (d, $^2J_{CP}$=11.17 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ=38.47; IR (film): ν=2973, 2944, 1606, 1438, 1220, 1123, 1033, 852, 794, 751, 730, 711, 696, 629, 576, 521 cm^{-1}; APCI-MS: *m/z* (%): 275.18 (100) $[M+H]^+$; HRMS: ($C_{16}H_{19}O_2P$: $[M+H]^+$) calcd: 275.1201, found: 275.1213.

4.1.2. Phenyl-(2,4,6-trimethylphenyl)-phosphinic acid ethyl ester (5b). Method B. *Step 1: diethyl-(2,4,6-trimethylphenyl)phosphonite*. Freshly prepared 2,4,6-trimethylphenyl magnesium bromide (prepared from 2-bromomesitylene (4.79 g, 24.05 mmol), magnesium (0.72 g, 30.07 mmol) and THF (30 ml)) was added to a solution of diethyl phosphorochloridite (3.17 g, 20.05 mmol) in THF (30 ml) at rt. After refluxing the mixture for 2 h, dioxane (43 ml) was added at rt and the mixture filtered. Evaporation in vacuo, and purification by Kugelrohr distillation gave the product (4.49 g, 93%) as a colourless oil; bp 130–132°C (0.3 mbar); ^1H NMR (400 MHz, $CDCl_3$): δ=1.33 (t, $^3J_{H-H}$=7.03 Hz, 6H), 2.30 (s, 3H), 2.65 (s, 6H), 3.99 (dq, $^3J_{H-P}$=9.14 Hz, $^3J_{H-H}$=7.02 Hz, 2H), 6.86 (d, $^4J_{H-P}$=1.93 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=17.37 (d, J_{CP}=6.0 Hz), 21.07, 21.65 (d, J_{CP}=20.1 Hz), 64.24 (d, J_{CP}=21.1 Hz), 129.66 (d, J_{CP}=4.0 Hz), 134.74 (d, J_{CP}=19.1 Hz), 139.92, 141.74 (d, J_{CP}=19.1 Hz); ^{31}P NMR (101.26 MHz, $CDCl_3$): δ=25.23; IR (film): ν=2974, 2927, 2875, 1605, 1442, 1385, 1097, 1056, 912, 743 cm^{-1}; APCI-MS: *m/z* (%): 241.2 (100) $[M+H]^+$, 213.1 (28) $[M-C_2H_4]^+$; HRMS: ($C_{13}H_{22}O_2P$: $[M+H]^+$) calcd: 241.1357, found: 241.1361.

Step 2: 2,4,6-trimethylphenylphosphinic acid ethyl ester (**9**). Diethyl 2,4,6-trimethylphenylphosphonite (4.3 g, 17.9 mmol) in THF (16 ml) was treated with 0.1 M HCl (35 ml), stirred at rt for 5 min, then heated to 50°C for 2.5 h. The reaction mixture was cooled to rt and extracted with CH_2Cl_2 (4×50 ml). The combined organic layers were dried over $MgSO_4$ and the solvents evaporated in vacuo to give **9** (3.62 g, 95%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$): δ=1.31 (part A_3 of A_3FGX system: dd, $^3J_{A-F}$=$^3J_{A-G}$=7.06 Hz, 3H), 2.21 (s, 3H), 2.49 (s, 6H), 4.06 (part F of A_3FGX system: dqd, $^3J_{F-P}$=8.88 Hz, $^3J_{F-A}$=7.00 Hz, $^2J_{F-G}$=10.08 Hz, 1H), 4.12 (part F of A_3FGX system: dqd, $^3J_{G-P}$=8.88 Hz, $^3J_{G-A}$=7.06 Hz, $^2J_{F-G}$=10.08 Hz, 1H), 6.80 (d, $^4J_{H-P}$=1.93 Hz, 2H), 7.86 (part G of A_3FGX system: d, $^1J_{H-P}$=551.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.16 (d, $^3J_{CP}$=6.0 Hz), 20.83, 20.96 (d, $^3J_{CP}$=34.2 Hz), 62.08 (d, $^2J_{CP}$=6.0 Hz), 123.08 (d, $^1J_{CP}$=67.4 Hz), 130.07 (d, $^3J_{CP}$=13.1 Hz), 141.71 (d, $^2J_{CP}$=11.1 Hz), 142.66 (d, $^4J_{CP}$=3.0 Hz); ^{31}P NMR (101.26 MHz, $CDCl_3$): δ=25.22; IR (film): ν=3469, 2978, 2926, 2366, 1606, 1453, 1222, 1089, 1035, 949, 633 cm^{-1}; APCI-MS: *m/z* (%): 213.15 (100) $[M+H]^+$; HRMS: ($C_{11}H_{18}O_2P$: $[M+H]^+$) calcd: 213.1044, found: 213.1046.

Step 3: phenyl-(2,4,6-trimethylphenyl)-phosphinic acid ethyl ester (**5b**). Iodobenzene (112 μl, 1 mmol), compound

9 (212 mg, 1 mmol), $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), Et_3N (0.45 ml, 3 mmol) and toluene (1.5 ml) were placed in a capped thick wall tube under Ar and heated to 100°C for 3.5 h. The mixture was allowed to cool to rt, diluted with EtOAc (20 ml) and filtered through celite. Evaporation in vacuo and purification by silica gel chromatography (EtOAc/petroleum spirit (40–60) 5/5) gave **5b** (231 mg, 80%) as a colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.34 (part A_3 of A_3FGX system: dd, $^3J_{A-F}$=7.09 Hz, $^3J_{A-G}$=7.23 Hz, 3H), 2.26 (s, 3H), 2.49 (d, 6H, $^4J_{H-P}$= 0.67 Hz), 4.04 (part F of A_3FGX system: dqd, $^3J_{F-P}$= 7.06 Hz, $^3J_{F-A}$=7.09 Hz, $^2J_{F-G}$=10.11 Hz, 1H), 4.13 (part G of A_3FGX system: dqd, $^3J_{G-P}$=7.22 Hz, $^3J_{G-A}$=7.23 Hz, $^2J_{F-G}$=10.11 Hz, 1H), 6.87 (d, $^4J_{H-P}$=3.97 Hz, 2H), 7.32–7.41 (m, 3H), 7.61–7.71 (dm, $^3J_{H-P}$=12.88 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=16.84 (d, $^3J_{CP}$=6.8 Hz), 21.47, 23.86 (d, $^3J_{CP}$=3.1 Hz), 60.66 (d, $^2J_{CP}$=5.8 Hz), 124.43 (d, $^1J_{CP}$=131.1 Hz), 128.76 (d, $^3J_{CP}$=13.3 Hz), 130.84 (d, $^2J_{CP}$=11.0 Hz), 131.18 (d, $^3J_{CP}$=13.1 Hz), 131.94 (d, $^4J_{CP}$=2.6 Hz), 134.89 (d, $^1J_{CP}$=134.5 Hz), 142.35 (d, $^4J_{CP}$=2.6 Hz), 144.09 (d, $^2J_{CP}$=11.3 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ=36.36; IR (film): ν= 2979, 2932, 1606, 1438, 1219, 1122, 1032, 950, 852, 750, 730, 710, 692, 630 cm^{-1}; APCI-MS: *m/z* (%): 289.21 (100) $[M+H]^+$; HRMS: ($C_{17}H_{22}O_2P$: $[M+H]^+$) calcd: 289.1357, found: 289.1347.

Alternative procedure using Pd(OAc)$_2$ and dppf: iodobenzene (112 μl, 1 mmol), compound **9** (212 mg, 1 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), dppf (74 mg, 0.13 mmol), Et_3N (0.28 ml, 2 mmol), acetonitrile (4.0 ml), 65°C for 21 h. Yield: 92% (265 mg).

Alternative procedure using K_3PO_4: Iodobenzene (112 μl, 1 mmol), compound **9** (212 mg, 1 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), K_3PO_4 (320 mg, 1.5 mmol), DMF (6.0 ml), 100°C for 22 h. Yield: 60% (180 mg).

4.1.3. Diphenylphosphinic acid methyl ester (7). Method A. H_3PO_2 (1 g, 15.15 mmol), trimethyl orthoformate (8.3 ml, 75.76 mmol), iodobenzene (3.4 ml, 30.5 mmol), $Pd(PPh_3)_2Cl_2$ (533 mg, 0.76 mmol), propylene oxide (10.5 ml, 150 mmol) and CH_3CN; purification by column chromatography (EtOAc/hexane: 8/2); yield: 2.25 g (64%) as colourless crystals; mp 50°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.78 (d, 3H, $^3J_{HP}$=11.01 Hz), 7.41–7.56 (m, 6H), 7.80–7.84 (dm, 2H, $^3J_{HP}$=12.26 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$): δ=51.95 (d, $^2J_{CP}$=5.9 Hz), 128.99 (d, $^3J_{CP}$=13.1 Hz), 131.42 (d, $^1J_{CP}$=137.1 Hz), 132.07 (d, $^2J_{CP}$=10.1 Hz), 132.64 (d, $^4J_{CP}$=2.8 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ=34.45; IR (film): ν=3058, 2949, 159, 1438, 1220, 1131, 1035, 998, 800, 753, 731, 696, 659, 561, 527 cm^{-1}; APCI-MS: *m/z* (%): 233.09 (100) $[M+H]^+$; HRMS: ($C_{13}H_{24}O_2P$: $[M+H]^+$) calcd: 233.0731, found: 233.0724.

4.1.4. Phenyl-2-tolyl-phosphinic acid methyl ester (8). Method A. 2-Iodotoluene (100 μl, 0.77 mmol), propylene oxide (670 μl, 9.6 mmol), crude phenylphosphinic acid methyl ester (100 mg, 0.64 mmol), $Pd(PPh_3)_4$ (prepared with sodium borohydride (3 mg, 0.08 mmol), triphenylphosphine (40 mg, 0.15 mmol) and $Pd(PPh_3)_2Cl_2$ (54 mg, 0.08 mmol), acetonitrile (3 ml) and benzene (3 ml)); purification by silica gel chromatography (EtOAc/hexane: 80/20) gave **8** (77 mg, 49%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.38 (s, 3H) 3.73 (d, 3H, $^3J_{H-P}$= 11.20 Hz), 7.15–7.18 (m, 1H), 7.25 (dt, 1H, $^5J_{H-P}$= 2.80 Hz, $^3J_{H-H}$=7.60 Hz), 7.37–7.43 (m, 3H), 7.47–7.51 (m, 1H), 7.71 (dm, 2H, $^3J_{H-P}$=12.40 Hz) 7.78 (ddd, 1H, $^3J_{H-P}$=12.80 Hz, $^3J_{H-H}$=7.60 Hz, $^4J_{H-H}$=0.80 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=21.18 (d, $^3J_{CP}$=4.43 Hz), 51.22 (d, $^2J_{CP}$=5.23 Hz), 125.49 (d, $^4J_{CP}$=12.28 Hz), 128.47 (d, $^3J_{CP}$=12.58 Hz), 128.82 (d, $^1J_{CP}$=135.44 Hz), 131.31 (d, $^1J_{CP}$=134.63 Hz), 131.45 (d, $^3J_{CP}$=13.38 Hz), 131.57 (d, $^2J_{CP}$=10.06 Hz), 132.08 (d, $^4J_{CP}$=2.62 Hz), 132.43 (d, $^3J_{CP}$=3.52 Hz), 133.18 (d, $^3J_{CP}$=9.36 Hz), 141.90 (d, $^2J_{CP}$=11.32 Hz); ^{31}P NMR (101.25 MHz, $CDCl_3$): δ= 36.36; APCI-MS: *m/z* (%): 247.12 (100) $[M+H]^+$; HRMS: ($C_{13}H_{24}O_2P$: $[M+H]^+$) calcd: 247.0888, found: 247.0896.

4.1.5. [4-(1,1-Dimethylethoxycarbonylamino)-phenyl]-(2,4,6-trimethyl phenyl)-phosphinic acid methyl ester (10a). Method A. H_3PO_2 (1.5 g, 22.7 mmol), trimethyl orthoformate (8.3 ml, 76 mmol), (4-iodophenyl)-carbamic acid *tert*-butyl ester (2.4 g, 7.6 mmol), $Pd(PPh_3)_2Cl_2$ (266 mg, 0.038 mmol), propylene oxide (5.3 ml, 76 mmol), acetonitrile/dioxane (16:4) then $Pd(PPh_3)_4$ (530 mg, 0.46 mmol), 2-iodomesitylene (1.1 g, 4.6 mmol), CH_3CN/benzene (15/7.5), Et_3N (6.5 ml, 46 mmol); purification by silica gel column chromatography (EtOAc/hexane: 7/3); yield: 320 mg (18%) as a white solid; mp 185°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.49 (s, 9H), 2.28 (s, 3H), 2.47 (s, 6H), 3.70 (d, 3H, $^3J_{P-H}$=11.20 Hz), 6.89 (d, $^4J_{H-P}$=3.60 Hz, 2H), 7.09 (s br, 1H), 7.42 (dd, 2H, $^4J_{H-P}$= 2.40 Hz, $^3J_{H-H}$=8.40 Hz), 7.55 (dd, 2H, $^3J_{H-P}$=12.40 Hz, $^3J_{H-H}$=8.80 Hz); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ= 21.07, 23.39 (d, $^3J_{CP}$=3.12 Hz), 28.24, 50.48 (d, $^2J_{CP}$= 6.54 Hz), 80.90, 117.74 (d, $^3J_{CP}$=13.88 Hz), 123.55 (d, $^1J_{CP}$=131.90 Hz), 127.17 (d, $^1J_{CP}$=141.16 Hz), 130.75 (d, $^3J_{CP}$=12.98 Hz), 131.67 (d, $^2J_{CP}$=12.58 Hz), 141.81 (d, $^4J_{CP}$=2.82 Hz), 141.97 (d, $^4J_{CP}$=2.82 Hz), 143.71 (d, $^2J_{CP}$=10.46 Hz), 152.41; ^{31}P NMR (101.25 MHz, $CDCl_3$): δ=38.48; IR (film): ν=3234, 2979, 2937, 1726, 1594, 1527, 1401, 1367, 1319, 1240, 1205, 1159, 1125, 1033, 909, 836, 796, 732, 684, 625, 576, 535 cm^{-1}; APCI-MS: *m/z* (%): 290.2 (100) $[M-C_5H_7O_2]^+$, 344.2 (31) $[M-C_4H_7]^+$, 390.2 (42) $[M+H]^+$; HRMS: ($C_{17}H_{22}O_2P$: $[M+H]^+$) calcd: 390.1834, found: 390.1830.

4.1.6. [4-(1,1-Dimethylethoxycarbonylamino)-phenyl]-(2,4,6-trimethyl phenyl)-phosphinic acid ethyl ester (10b). Method B. Step 3. (4-Iodo-phenyl)-carbamic acid *tert*-butyl ester (638 mg, 2 mmol), compound **9** (424 mg, 2 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), Et_3N (0.85 ml, 6 mmol), CH_3CN (3 ml); purification by silica gel chromatography (EtOAc/petroleum spirit: 40/60) gave compound **10b** (302 mg, 38%) as a white solid; mp 183°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.37 (part A of A_3FGX system: dd, $^3J_{A-F}$=7.12 Hz, $^3J_{A-G}$=7.16 Hz 3H), 1.53 (s, 9H), 2.32 (s, 3H), 2.52 (s, 6H), 4.07 (part F of A_3FGX system: dqd, $^3J_{F-P}$=7.12 Hz, $^3J_{F-A}$=7.12 Hz, $^2J_{F-G}$=10.15 Hz, 1H), 4.13 (part G of A_3FGX system: dqd, $^3J_{G-P}$=7.19 Hz, $^3J_{G-A}$= 7.16 Hz, $^2J_{G-F}$=10.15 Hz, 1H), 6.92 (d, $^4J_{H-P}$=3.50 Hz, 2H), 7.28 (s br, 1H), 7.47 (dd, 2H, $^4J_{H-P}$=2.50 Hz, $^3J_{H-H}$= 8.50 Hz), 7.60 (dd, 2H, $^3J_{H-P}$=12.50 Hz, $^3J_{H-H}$=8.50 Hz);

^{13}C NMR (125.72 MHz, $CDCl_3$): δ=16.86 (d, $^3J_{CP}$=7.17 Hz), 21.50, 23.96 (d, $^3J_{CP}$=3.20 Hz), 28.72, 60.62 (d, $^2J_{CP}$=6.03 Hz), 81.25, 118.24 (d, $^3J_{CP}$=12.57 Hz), 124.82 (d, $^1J_{CP}$=132.76 Hz), 128.14 (d, $^1J_{CP}$=137.91 Hz), 131.17 (d, $^3J_{CP}$=12.57 Hz), 132.13 (d, $^2J_{CP}$=12.45 Hz), 142.24, 144.01 (d, $^2J_{CP}$=11.69 Hz), 152.96; ^{31}P NMR (202.39 MHz, $CDCl_3$): δ=36.41; IR (film): ν=2982, 2930, 1718, 1604, 1518, 1401, 1368, 1318, 1242, 1159, 1032, 909, 835, 733, 683, 649, 576 cm^{-1}; APCI-MS: *m/z* (%): 304.2 (100) $[M-C_5H_8O_2]^+$, 404.2 (29) $[M+H]^+$; HRMS: ($C_{17}H_{22}O_2P$: $[M+H]^+$) calcd: 404.1991, found: 404.2000.

4.1.7. 4-(4-Methoxycarbonylbutyl)-phenyl-(2,4,6-trimethylphenyl)-phosphinic acid methyl ester (11a). Method A. H_3PO_2 (360 mg, 5.5 mmol), trimethyl orthoformate (2.0 ml, 18.4 mmol), compound **15** (0.58 g, 1.8 mmol), $Pd(PPh_3)_2Cl_2$ (580 mg, 0.092 mmol), propylene oxide (1.3 ml, 18.4 mmol), CH_3CN (5 ml) then $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol), 2-iodomesitylene (450 mg, 1.8 mmol), CH_3CN (5 ml), propylene oxide (1.3 ml, 18.4 mmol); purification by silica gel column chromatography (EtOAc/hexane: 7/3); yield: 143 mg (20%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.66–1.68 (m, 4H), 2.32 (s, 3H), 2.35 (t, 3H, $^3J_{H-H}$=7.00 Hz), 2.52 (s, 6H), 2.67 (t, 2H, $^3J_{H-H}$=7.25 Hz), 3.69 (s, 3H), 3.75 (d, $^3J_{P-H}$=11.00 Hz, 3H), 6.93 (d, $^4J_{H-P}$=4.00 Hz, 2H), 7.24 (dd, 2H, $^4J_{H-P}$=3.50 Hz, $^3J_{H-H}$=8.00 Hz), 7.60 (dd, 2H, $^3J_{H-P}$=12.50 Hz, $^3J_{H-H}$=8.00 Hz); ^{13}C NMR (125.72 MHz, $CDCl_3$): δ=21.52, 23.80, 24.89, 30.92, 34.25, 35.98, 50.96 (d, $^2J_{CP}$=5.78 Hz), 51.94, 123.99 (d, $^1J_{CP}$=129.36 Hz), 128.93 (d, $^3J_{CP}$=12.07 Hz), 131.03 (d, $^2J_{CP}$=10.56 Hz), 131.21 (d, $^3J_{CP}$=10.69 Hz), 131.63 (d, $^1J_{CP}$=138.79 Hz), 142.44, 144.26 (d, $^2J_{CP}$=12.95 Hz), 146.65, 174.3; ^{31}P NMR (202.39 MHz, $CDCl_3$): δ=38.80; IR (film): ν=2946, 2869, 1737, 1605, 1438, 1220, 1120, 1032, 852, 786, 681, 661, 624, 575 cm^{-1}; APCI-MS: *m/z* (%): 389.20 (100) $[M+H]^+$; HRMS: ($C_{22}H_{29}O_4P$: $[M+H]^+$) calcd: 389.1882, found: 389.1868.

4.1.8. 4-(4-Methoxycarbonylbutyl)-phenyl-(2,4,6-trimethylphenyl)-phosphinic acid ethyl ester (11b). Method B. Step 3. With compound **15** (950 mg, 3.0 mmol), compound **9** (635 mg, 3.0 mmol), $Pd(PPh_3)_4$ (345 mg, 0.3 mmol), Et_3N (1.3 ml, 9.0 mmol) and toluene (4.5 ml); purification by silica gel chromatography (EtOAc/petroleum spirit: 40/60) gave **11b** (546 mg, 45%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (part A of A_3FGX system: dd, $^3J_{A-F}$=7.10 Hz, $^3J_{A-G}$=7.17 Hz, 3H), 1.63 (m, 4H), 2.27 (s, 3H), 2.31 (t, 3H, $^3J_{H-H}$=7.20 Hz), 2.49 (s, 6H), 2.63 (t, 2H, $^3J_{H-H}$=7.20 Hz), 3.64 (s, 3H), 4.03 (part F of A_3FGX system: dqd, $^3J_{F-P}$=7.05 Hz, $^3J_{F-A}$=7.10 Hz, $^2J_{F-G}$=10.05 Hz), 4.12 (part G of A_3FGX system: dqd, $^3J_{G-P}$=7.15 Hz, $^3J_{G-A}$=7.17 Hz, $^2J_{G-F}$=10.05 Hz, 1H), 6.88 (d, $^4J_{H-P}$=4.00 Hz, 2H), 7.19 (dd, 2H, $^4J_{H-P}$=3.30 Hz, $^3J_{H-H}$=8.20 Hz), 7.56 (dd, 2H, $^3J_{H-P}$=12.60 Hz, $^3J_{H-H}$=7.40 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=16.43 (d, $^3J_{CP}$=6.8 Hz), 21.05, 23.46 (d, $^3J_{CP}$=3.2 Hz), 24.43, 30.47, 33.79, 35.52, 51.47, 60.17 (d, $^2J_{CP}$=5.6 Hz), 124.24 (d, $^1J_{CP}$=131.5 Hz), 128.41 (d, $^3J_{CP}$=13.7 Hz), 130.57 (d, $^2J_{CP}$=11.9 Hz), 130.70 (d, $^3J_{CP}$=13.4 Hz), 131.67 (d, $^1J_{CP}$=137.3 Hz), 141.78 (d, $^4J_{CP}$=3.3 Hz), 143.64 (d, $^2J_{CP}$=11.64 Hz), 146.00 (d, $^4J_{CP}$=2.4 Hz), 173.89; ^{31}P NMR (101.25 MHz, $CDCl_3$): δ=36.72; IR (film): ν=2978, 2935, 1737, 1605, 1438, 1220, 1120, 1033, 950, 852, 781, 680, 659, 626, 576, 514 cm^{-1}; APCI-MS: *m/z* (%): 403.29 (100) $[M+H]^+$; HRMS: ($C_{17}H_{22}O_2P$: $[M+H]^+$) calcd: 403.2038, found: 403.2038; second product, identified as phenyl-(2,4,6-trimethylphenyl)-phosphinic acid ethyl ester **5b** was also isolated in 25% (217 mg, 0.75 mmol).

For an alternative procedure using using $Pd(OAc)_2$ and dppf: compound **14** (318 mg, 1.0 mmol), compound **9** (212 mg, 1.0 mmol), $Pd(OAc)_2$ (17 mg, 0.07 mmol), DPPF (74 mg, 0.13 mmol), Et_3N (0.28 ml, 2.0 mmol) acetonitrile (4.0 ml), 65°C for 19 h. Yield: 48% (193 mg).

4.1.9. Phenyl-(2,4,6-trimethoxyphenyl)-phosphinic acid ethyl ester (12). Method B. *Step 1: diethyl(2,4,6-trimethoxyphenyl)phosphonite*: 2.1 M *n*BuLi in *n*-hexane (7 ml, 14.8 mmol) was added dropwise to a suspension of 1,3,5-trimethoxybenzene (5 g, 29.7 mmol) and TMEDA (2.2 ml, 14.8 mmol) in pentane (30 ml) and the resulting mixture stirred at rt overnight. The formed precipitate was filtered and washed with pentane (20 ml), and solubilised in Et_2O (10 ml). A solution of diethylchlorophosphite (2.1 ml, 14.8 mmol) in Et_2O (5 ml) was added dropwise at 0°C. The mixture stirred at rt for 24 h. Dioxane (30 ml) was added to the solution, which was filtered. Evaporation in vacuo and purification by Kugelrohr distillation gave 1.86 g of product (43%) as a colourless oil; bp: 158–160°C (0.3 mbar).

Step 2: (2,4,6-trimethoxyphenyl)-phosphinic acid ethyl ester: diethyl(2,4,6-trimethoxyphenyl)phosphonite (1.57 g, 5.45 mmol), THF (5 ml), 0.1 M HCl (10 ml), 50°C for 2.5 h. The reaction mixture was cooled to rt and extracted with CH_2Cl_2 (4×20 ml); yield: 1.39 g (98%) as a white solid; mp 52°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.36 (t, $^3J_{H-H}$=7.25 Hz, 3H), 3.83 (s, 9H), 4.16 (dq, $^3J_{P-H}$=9.00 Hz, $^3J_{H-H}$=7.12 Hz, 2H), 6.08 (d, $^4J_{H-P}$=4.50 Hz, 2H), 7.85 (d, 1H, $^1J_{H-P}$=592.48 Hz); ^{13}C NMR (125.72 MHz, $CDCl_3$): δ=16.77 (d, $^3J_{CP}$=6.91 Hz), 56.35, 62.24 (d, $^2J_{CP}$=5.78 Hz), 90.99 (d, $^3J_{CP}$=4.90 Hz), 99.79 (d, $^1J_{CP}$=137.79 Hz), 164.55, 165.98; ^{31}P NMR (101.25 MHz, $CDCl_3$): δ=20.57; IR (film): ν=2979, 2942, 2403, 1600, 1579, 1459, 1437, 1413, 1340, 1230, 1208, 1161, 1131, 1111, 1047, 953, 815, 730, 644 cm^{-1}; APCI-MS: *m/z* (%): 261.11 (100) $[M+H]^+$; HRMS: ($C_{11}H_{18}O_5P$: $[M+H]^+$) calcd: 261.0892, found: 261.0900.

Step 3: phenyl-(2,4,6-trimethoxyphenyl)-phosphinic acid ethyl ester (**12**): iodobenzene (204 mg, 1 mmol), (2,4,6-trimethoxyphenyl)-phosphinic acid ethyl ester (260 mg, 1 mmol), $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), Et_3N (0.45 ml, 3 mmol), toluene (2.5 ml); 100°C overnight; purification by silica gel chromatography (EtOAc/MeOH: 96/4); yield: 249 mg (74%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (part A of A_3FGX system: dd, $^3J_{A-F}$=7.15 Hz, $^3J_{A-G}$=7.15 Hz, 3H), 3.60 (s, 6H), 3.76 (s, 3H), 4.06 (part F of A_3FGX system: dqd, $^3J_{F-P}$=7.15 Hz, $^3J_{F-A}$=7.15 Hz, $^2J_{F-G}$=10.10 Hz, 1H), 4.13 (part G of A_3FGX system: dqd, $^3J_{G-P}$=7.05 Hz, $^3J_{G-A}$=7.15 Hz, $^2J_{G-F}$=10.10 Hz, 1H), 6.01 (d, $^4J_{H-P}$=4.40 Hz, 2H), 7.31–7.41 (m, 3H), 7.73–7.76 (dm, $^3J_{H-P}$=12.80 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=16.51 (d, $^3J_{CP}$=7.04 Hz), 55.28, 55.73, 60.57 (d, $^2J_{CP}$=6.04 Hz), 91.02 (d, $^3J_{CP}$=

8.05 Hz), 100.22 (d, $^{1}J_{CP}$=139.86 Hz), 127.59 (d, $^{3}J_{CP}$= 13.08 Hz), 130.57 (d, $^{2}J_{CP}$=10.06 Hz), 130.72 (d, $^{4}J_{CP}$= 3.02 Hz), 135.76 (d, $^{1}J_{CP}$=146.91 Hz), 164.29 (d, $^{2}J_{CP}$= 2.01 Hz), 164.97; ^{31}P NMR (101.25 MHz, $CDCl_3$): δ= 31.29; FT-IR (film): ν=2979, 2940, 1600,1577, 1467 (s), 1438, 1410, 1340, 1230, 1208, 1162, 1123, 1100, 1038, 955, 815, 750, 736, 718, 697, 545, 526 cm^{-1}; APCI-MS: *m/z* (%): 337.16 (100) $[M+H]^+$; HRMS: ($C_{17}H_{22}O_5P$: $[M+H]^+$) calcd: 337.1205, found: 337.1201.

4.1.10. (2-Methylphenyl)-(2,4,6-trimethylphenyl)-phosphinic acid ethyl ester (13). Method B. 2-Iodotoluene (114 μl, 1.1 mmol), compound **9** (212 mg, 1 mmol), $Pd(PPh_3)_3$ (115 mg, 0.05 mmol), Et_3N (0.42 ml, 3 mmol) and toluene (3 ml); 110°C for 3 days; purification by silica gel chromatography (EtOAc/petroleum spirit (40–60) 5/5); yield: 100 mg (33%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.40 (part A of A_3FGX system: dd, $^{3}J_{A-F}$=7.06 Hz, $^{3}J_{A-G}$=7.08 Hz, 3H), 2.33 (s, 3H), 2.42 (s, 3H), 2.50 (s, 6H), 4.02 (part F of A_3FGX system: dqd, $^{3}J_{F-P}$=7.06 Hz, $^{3}J_{F-A}$=7.06 Hz, $^{2}J_{F-G}$=9.97 Hz, 1H), 4.18 (part G of A_3FGX system: dqd, $^{3}J_{G-P}$=7.12 Hz, $^{3}J_{G-A}$= 7.08 Hz, $^{2}J_{G-F}$=9.97 Hz, 1H), 6.92 (d, $^{4}J_{H-P}$=3.50 Hz, 2H), 7.20–7.26 (m, 2H), 7.39 (t, $^{3}J_{H-H}$=7.50 Hz, 1H), 7.76 (ddd, $^{3}J_{H-P}$=14.00 Hz, $^{3}J_{H-H}$=7.50 Hz, $^{4}J_{H-H}$=1.00 Hz, 1H); ^{13}C NMR (125.72 MHz, $CDCl_3$): δ=16.85 (d, $^{3}J_{CP}$=5.40 Hz), 21.06 (d, $^{3}J_{CP}$=3.52 Hz), 21.51, 23.76 (d, $^{3}J_{CP}$=1.76 Hz), 60.44 (d, $^{2}J_{CP}$=6.35 Hz), 125.15 (d, $^{1}J_{CP}$=131.26 Hz), 125.74 (d, $^{3}J_{CP}$=15.09 Hz), 131.26 (d, $^{3}J_{CP}$=11.69 Hz), 131.79 (d, $^{2}J_{CP}$=12.19 Hz), 132.05, 132.61 (d, $^{2}J_{CP}$= 11.06 Hz), 132.92 (d, $^{1}J_{CP}$=131.16 Hz), 141.56 (d, $^{2}J_{CP}$= 10.94 Hz) 142.21, 144.02 (d, $^{2}J_{CP}$=13.07 Hz); ^{31}P NMR (202.40 MHz, $CDCl_3$): δ=36.58; FT-IR (film): ν=2979, 2932, 1606, 1454, 1218, 1029, 949, 852, 755, 691, 629, 581 cm^{-1}; APCI-MS: *m/z* (%): 303.2 (100) $[M+H]^+$; HRMS: ($C_{18}H_{23}O_2P$: $[M+H]^+$) calcd: 303.1514, found: 303.1524.

4.1.11. Methyl 5-(4-iodophenyl) pentanoate (14). Methyl 5-phenylvalerate(1.7 g, 8.8 mmol) was dissolved in trifluoroacetic acid (35 ml) containing $Tl(OOCCF_3)_3$ (4.8 g, 8.8 mmol) and stirred for 5 days at rt in the dark. Potassium iodide (7.3 g, 12.9 mmol) in water (55 ml) was added and the mixture stirred for 15 min, sodium thiosulfate (1.4 g) was then added and the mixture stirred for 15 min. The mixture was poured into water (250 ml) and extracted with ether. The combined organic layers were washed with aqueous HCl (0.1N, 3×250 ml), water (4×250 ml) and dried ($MgSO_4$). Evaporation in vacuo and purification by column chromatography (petroleum spirit (40–60)/ EtOAc: 9/1) gave **15** (2.6 g, 93%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.66–1.70 (m, 4H), 2.38 (t, 2H, ^{3}J=6.50 Hz), 2.62 (t, 2H, ^{3}J=7.25 Hz), 3.71 (s, 3H), 6.98 (d, 2H, ^{3}J=8.00 Hz), 7.64 (d, 2H, ^{3}J=8.00 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=24.9, 31.1, 34.3, 35.5, 52.0, 91.2, 131.0, 137.8, 142.2, 174.4 (*C*O); FT-IR (film): ν=2946, 2859, 1737, 1485, 1435, 1200, 1173, 1006 cm^{-1}; GC–MS (CI+): *m/z* (%): 336.0 (100) $[M+NH_4]^+$; HRMS: ($C_{12}H_{15}IO_2$): $[M+NH_4]^+$) calcd: 336.0461, found: 336.0469.

4.1.12. 4-(4-Hydroxycarbonylbutylphenyl)-2,4,6-trimethylphenyl-phosphinic acid (4b). Bromotrimethylsilane (1.1 ml, 8.5 ml) was added to a solution of **11b** (471 mg, 1.17 mmol) in CH_2Cl_2 (4.5 ml). The mixture was stirred for 2 h at rt then methanol (5 ml) was added. The solvents were evaporated and the crude dissolved in dioxane (4.5 ml). A solution of 1 M aq. LiOH (8.5 ml) was added, and the mixture stirred for 5 h at rt. The aqueous phase was acidified (pH=1) with a 1 M HCl solution, extracted with chloroform and the combined organic layers dried (Na_2SO_4). Evaporation in vacuo and purification by silica gel column chromatography (EtOAc 100%→EtOAc/CH_2Cl_2/MeOH: 5/5/0.5) gave **4** (265 mg, 63%) as a white solid; mp 85°C; *Rf*=0.1 (EtOAc/CH_2Cl_2: 50/50); ^{1}H NMR (500 MHz, MeOH-d_4, TFA-d): δ=7.57 (dd, 2H, J_{H-H}=7.6 Hz, J_{P-H}=12.8 Hz), 7.29 (dd, 2H, J_{H-H}= 7.5 Hz, J_{P-H}=2.7 Hz), 6.94 (d, 2H, J_{P-H}=3.5 Hz), 2.68 (t, 2H, J_{H-H}=6 Hz), 2.48 (s, 6H), 2.34 (t, 2H, J_{H-H}=7 Hz), 2.28 (s, 3H), 1.64 (m, 4H); ^{13}C NMR (125.7 MHz, MeOH-d_4, TFA-d): δ=174.9, 146.8, 143.4 (d, J_{CP}=10.3 Hz), 142.4, 132.3 (d, J_{CP}=136.2 Hz), 130.7 (d, J_{CP}=15.72 Hz), 130.3 (d, J_{CP}= 13.1 Hz), 128.6 (d, J_{CP}=11.2 Hz), 125.5 (d, J_{CP}=135.2 Hz), 35.4, 33.5, 30.6, 24.5, 22.8, 20.1; ^{31}P NMR (202.4 MHz, MeOH-d_4, TFA-d): δ=34.94; FT-IR (film): ν=2979, 2942, 2403, 1600, 1579, 1459, 1437, 1413, 1340, 1230, 1208, 1161, 1131, 1111, 1047, 953, 815, 730, 644 cm^{-1}; APCI-MS: *m/z* (%): 361.21 (100) $[M+H]^+$; HRMS: ($C_{20}H_{26}O_4P$: $[M+H]^+$) calcd: 361.1569, found: 361.1566.

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