



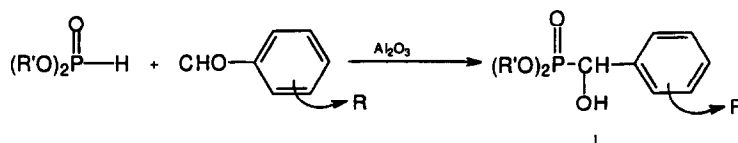
The Facile Synthesis of *O,O*-Dialkyl α -halobenzylphosphonates from *O,O*-Dialkyl α -hydroxybenzylphosphonates

Donovan Green*, Said Elgendy, Geeta Patel, Jehan A. Baban, Emmanuel Skordalakes, Wahid Husman, Vijay V. Kakkar and John Deadman

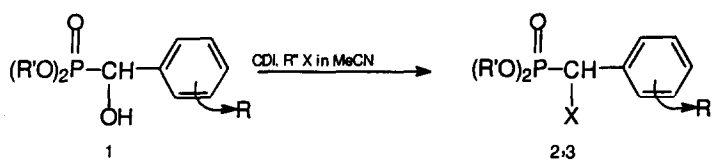
Thrombosis Research Institute, Emmanuel Kaye Building, Manresa Road, Chelsea SW3 6LR, UK

Abstract: *O,O*-Dialkyl α -hydroxybenzylphosphonates (1) can be easily converted in their corresponding α -bromo (2) or α -iodo (3) phosphonates, in quantitative yield, using *N,N'*-carbonyldiimidazole (CDI) in the presence of allyl bromide or methyl iodide. Copyright © 1996 Elsevier Science Ltd

O,O-Dialkyl α -hydroxyphosphonates¹ (1, Table 1 - prepared by the reaction of aldehyde and dialkyl phosphite on Al_2O_3 , Scheme 1²), have attracted considerable interest due to their efficacy in a number of biological systems.³ The compounds are useful substrates for conversion into a variety of biologically and pharmaceutically useful α - functionalised phosphonates.⁴ Although a range of substrates procedures exist for the conversion of alcoholic moieties into the corresponding halofunction,⁵ these methods are not readily applicable to α - hydroxyphosphonates.⁶ We report that *O,O*-dialkyl α -hydroxybenzylphosphonates may be smoothly converted to their corresponding α -halobenzylphosphonates (2, Table 2 and 3, Table 3) by using *N,N'*-carbonyldiimidazole (CDI) in the presence of excess allyl bromide or methyl iodide at room temperature for 30 mins followed by 150°C for 4h, with anhydrous acetonitrile as the solvent for the reaction (Scheme 2).⁷



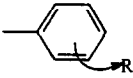
Scheme 1



Scheme 2

The α -halobenzylphosphonates were generally isolated in quantitative yield (except for *O,O*-dimethyl and *O,O*-dibenzyl derivatives, whose α -hydroxy analogues are known to be unstable⁸) as clear (2) or slightly reddish-brown (3) viscous oils.

Table 1 *O,O*-DIALKYL α -HYDROXYBENZYLPHOSPHONATES

Entry	R'		¹³ C(CDCl ₃) $\delta_{\alpha\text{C}}(^1\text{J}_{\text{PC}})$	³¹ P(CDCl ₃) δ/ppm	FABMS %(3-NOBA)
1	CH ₃ (CH ₂) ₃	4-CH ₃ O	70.34(161.37)	22.35	331, M+H(10.88)
2	CH ₃ CH ₂	4-CH ₃ CH ₂ O	70.30(161.69)	22.50	289, M+H(18.34)
3	(CH ₃) ₂ CH	4-CH ₃ CH ₂ O	70.61(159.56)	20.83	317, M+H(20.88)
4	CH ₃ CH ₂	2,3,4-(CH ₃ O) ₃	65.20(163.75)	22.93	335, M+H(25.00)
5	(CH ₃) ₂ CH	3-CH ₃ CH ₂ O,4-CH ₃ O	70.73(162.97)	20.92	347, M+H(16.47)

The ¹H N.M.R. spectra of the α -halobenzylphosphonates were initially characterised by the appearance of a sharp doublet at approximately 5.00 ppm for the P-CH region of the molecule. This followed the disappearance of the complex multiplicities observed earlier in the same region of the spectrum for the P-CH(OH) interactions in the starting material.

Table 2 *O,O*-DIALKYL α -BROMOBENZYLPHOSPHONATES

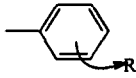
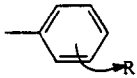
Entry	R'		$^{13}\text{C}(\text{CDCl}_3)$ $\delta\alpha\text{C}(^1\text{J}_{\text{PC}})$	$^{31}\text{P}(\text{CDCl}_3)$ δ/ppm	FABMS %(3-NOBA)
1	$\text{CH}_3(\text{CH}_2)_3$	4- CH_3O	41.51(162.18)	17.77	394, M+H(4.45)
2	CH_3CH_2	4- $\text{CH}_3\text{CH}_2\text{O}$	41.57(162.00)	17.89	375, M+H+Na(62.0)
3	$(\text{CH}_3)_2\text{CH}$	4- $\text{CH}_3\text{CH}_2\text{O}$	42.28(163.51)	16.28	380, M+H(1.94)
4	CH_3CH_2	2,3,4- $(\text{CH}_3\text{O})_3$	33.88(165.80)	18.47	398, M+H(2.50)
5	$(\text{CH}_3)_2\text{CH}$	3- $\text{CH}_3\text{CH}_2\text{O}$, 4- CH_3O	42.62(163.87)	16.34	410, M+H(13.67)

Table 3 *O,O*-DIALKYL α -IODOBENZYLPHOSPHONATES

Entry	R'		$^{13}\text{C}(\text{CDCl}_3)$ $\delta\alpha\text{C}(^1\text{J}_{\text{PC}})$	$^{31}\text{P}(\text{CDCl}_3)$ δ/ppm	FABMS %(3-NOBA)
1	$\text{CH}_3(\text{CH}_2)_3$	4- CH_3O	15.30(158.36)	19.45	463, M+Na(12.06)
2	CH_3CH_2	4- $\text{CH}_3\text{CH}_2\text{O}$	15.43(158.44)	19.57	399, M+H(15.56)
3	$(\text{CH}_3)_2\text{CH}$	4- $\text{CH}_3\text{CH}_2\text{O}$	16.80(160.14)	18.02	449, M+Na(82.94)
4	CH_3CH_2	2,3,4- $(\text{CH}_3\text{O})_3$	15.19(162.69)	20.11	468, M+H+Na(3.89)
5	$(\text{CH}_3)_2\text{CH}$	3- $\text{CH}_3\text{CH}_2\text{O}$, 4- CH_3O	17.03(160.20)	17.94	457, M+H(8.34)

NB The alkoxycarbonylimidazole intermediate formed at R.T. by the reaction of the α -hydroxyphosphonate and N,N' -carbonyl-diimidazole is quaternized with reactive halide (e.g. allyl bromide or methyl iodide), to form a substituted imidazole phosphonate salt. Heating this intermediate to 150°C was found to favour formation of a phosphonate carbenium ion with decarboxylation, which readily combines with halide ions to give the α -halophosphonate.⁷

The magnetic non-equivalence of the *O,O*-dialkyl groups (due to restricted rotation about the phosphorus-carbon bond) were unaffected and compared favourably with the feature observed in α -hydroxybenzylphosphonates⁹ and α -benzylaminobenzylphosphonates.¹⁰ Similarly, in the ¹³C N.M.R. spectra, the highly characteristic P-C α doublet moved significantly upfield from around 70 ppm in the substrate (1), to approximately 40 ppm for the α -bromo analogues, and approximately 15 ppm for the α -iodo compounds. Multiple signals were also observed due to chemical shift non-equivalence of the dialkoxy region. As shown in the Tables, concomitant variations were also observed in the ³¹P N.M.R. spectra, where the ³¹P chemical shifts of the products were markedly different from those of the starting materials.

The FAB mass spectra of compounds 2 and 3 (run in a matrix of 3-nitrobenzyl alcohol) displayed their definitive [M+H]⁺ or [M+Na]⁺ peaks, in addition to a highly abundant signal corresponding to [M+H-HX]⁺. This latter fragment was also observed in the other α -halobenzylphosphonates, and was sometimes the base peak. However unlike dialkyl α -hydroxyphosphonates, dialkyl α -benzylaminophosphonates, dialkyl α -aminophosphonates and α -aminophosphonic acids,¹¹ no fragment was observed for P-C α cleavage.

In our investigations of substrate-derived isosteric peptides as thrombin inhibitors,^{12,13} α -haloalkyl boronic acid esters,¹⁴ have been used in our laboratory to produce a series of 'fibrinogen-like' peptides possessing a surrogate peptide bond. These compounds displayed potent inhibition toward thrombin.¹⁵ It is envisaged that *O,O*-dialkyl α -halobenzylphosphonates may be similarly tethered to peptides based upon the 'Phe-Pro-Arg' sequence, so that they too may become useful precursors of novel anti-thrombotic agents. The method of preparation described also provides a useful substrate for conversion into other α -functionalised phosphonates of chemical and biological significance.

EXPERIMENTAL

The phosphonates (1,2 and 3) were fully characterised by ¹H, ¹³C and ³¹P high field N.M.R. Their FAB mass spectra (in a matrix of 3-nitrobenzyl alcohol) were obtained with a Vacuum Generator (VG) Analytical ZAB-E spectrometer with a primary beam of xenon atoms generated in an ion gun operating at 8kv. C, H, N values were obtained using a Carlo Erba Model 1106 Elemental Analyser.

General method for preparation of *O,O*-dialkyl α -hydroxybenzylphosphonates

Aromatic aldehyde (0.05 mol) and dialkyl phosphite (0.05 mol) were mixed together with vigorous stirring for 10 min, under argon. Al₂O₃ (30g) was added to the clear solution and shaken to ensure uniform absorption onto

the support. The solid that had formed, became very hot, and was allowed to stand at R.T. for 48h. The material was suspended in excess CH_2Cl_2 and filtered off to remove Al_2O_3 . The filtrate was concentrated under reduced pressure to afford a white (or sometimes brightly colored) waxy solid in quantitative yield. Analytical data is given below for a few of the examples prepared.

O,O-Diethyl α -hydroxy 4-ethoxybenzylphosphonate: $\text{C}_{13}\text{H}_{21}\text{O}_5\text{P}$ Found C- 53.89, H- 7.34%; $\text{C}_{13}\text{H}_{21}\text{O}_5\text{P}$ requires C- 53.98, H- 7.27%; $^1\text{H}(\text{CDCl}_3)$: δ 1.18-1.27 (2xt, 6H, $\text{CH}_3\text{CH}_2\text{Ox2}$, $^3J_{\text{HCCH}}$ 7.06, $^3J_{\text{HCCH}}$ 7.08), 1.40 (t, 3H, OCH_2CH_3 , $^3J_{\text{HCCH}}$ 7.02), 3.90-4.14 (m, 6H, $\text{CH}_3\text{CH}_2\text{Ox2}$ overlapping OCH_2CH_3), 4.70-4.74 (m, 1H, P- CHOH), 4.91-4.95 (m, 1H, P- CHOH), 6.86 (d, 2H, H_{ortho} , $^3J_{\text{HCCH}}$ 8.62), 7.39 (d, 2H, H_{para} , $^3J_{\text{HCCH}}$ 8.74); $^{13}\text{C}(\text{CDCl}_3)$: δ 14.82 (s, OCH_2CH_3), 16.40 (dd, $\text{CH}_3\text{CH}_2\text{Ox2}$, $^3J_{\text{POCC}}$ 4.60), 63.10 (dd, $\text{CH}_3\text{CH}_2\text{Ox2}$, $^2J_{\text{POC}}$ 7.07), 63.39 (s, OCH_2CH_3), 70.30 (d, P- CH , $^1J_{\text{PC}}$ 161.69), 114.21 (d, C_{ortho} , $^3J_{\text{PCCC}}$ 1.81), 128.52 (s, C_{meta}), 158.80 (d, C_1 , $^2J_{\text{PCC}}$ 2.91); $^{31}\text{P}(\text{CDCl}_3)$: δ 22.50 (s); FABMS(3-NOBA): $m/z(\%)$ 311 ($[\text{M}+\text{Na}]^+$, 28.28), 289 ($[\text{M}+\text{H}]^+$, 18.34), 151 ($[\text{M}+\text{H} - (\text{EtO})_2\text{P}(\text{O})\text{H}]^+$, 76.47).

O,O-Di-n-butyl α -hydroxy 4-methoxybenzylphosphonate: $\text{C}_{16}\text{H}_{27}\text{O}_5\text{P}$ requires C- 58.18, H- 8.18%; $^1\text{H}(\text{CDCl}_3)$: δ 0.85-0.94 (m, 6H, terminal CH_3 's), 1.24-1.62 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{Ox2}$), 3.80 (s, 3H, OCH_3), 3.85-4.02 (m, 4H, CH_2O), 4.68 (s, br, 1H, P- CHOH), 4.95 (d, 1H, P- CHOH , $^2J_{\text{PCH}}$ 10.24), 6.87 (d, 2H, H_{ortho} , $^3J_{\text{HCCH}}$ 8.66), 7.40 (d, 2H, H_{meta} , $^3J_{\text{HCCH}}$ 8.74); $^{13}\text{C}(\text{CDCl}_3)$: δ 13.59 (s, terminal CH_3), 13.61 (s, terminal CH_3), 18.61 (s, CH_2CH_3), 18.65 (s, CH_2CH_3), 32.54 (dd, $\text{CH}_2\text{CH}_2\text{CH}_3$, $^3J_{\text{POCC}}$ 2.61), 55.24 (s, OCH_3), 66.76 (dd, OCH_2 , $^2J_{\text{POC}}$ 7.47), 70.34 (d, P- CH , $^1J_{\text{PC}}$ 161.37), 113.64 (d, C_{ortho} , $^3J_{\text{PCCC}}$ 1.80), 128.53 (s, C_{meta}), 159.40 (d, C_1 , $^2J_{\text{PCC}}$ 2.73); $^{31}\text{P}(\text{CDCl}_3)$: δ 22.35 (s); FABMS(3-NOBA): $m/z(\%)$ 331 ($[\text{M}+\text{H}]^+$, 10.88), 137 ($[\text{M}+\text{H}-(\text{C}_4\text{H}_9\text{O})_2\text{P}(\text{O})\text{H}]^+$, 100).

O,O-Diisopropyl α -hydroxy 3-ethoxy, 4-methoxybenzylphosphonate: $\text{C}_{16}\text{H}_{27}\text{O}_6\text{P}$ Found C- 55.32, H- 7.90%; $\text{C}_{16}\text{H}_{27}\text{O}_6\text{P}$ requires C- 55.49, H- 7.80%; $^1\text{H}(\text{CDCl}_3)$: δ 1.25-1.29 (m, 12H (CH_3) $_2\text{CHOx2}$), 1.45 (t, 3H, OCH_2CH_3 , $^3J_{\text{HCCH}}$ 7.01), 3.86 (s, 3H, OCH_3), 4.10 (q, 2H, OCH_2CH_3 , $^3J_{\text{HCCH}}$ 7.01), 4.55-4.69 (m, 2H, (CH_3) $_2\text{CHOx2}$), 4.85-4.95 (m, 2H, P- CHOH), 6.82 (d, 1H, H_5 of aromatic ring, $^3J_{\text{HCCH}}$ 8.29), 6.98 (m, 1H, H_6 of aromatic ring), 7.13 (s, 1H, H_2 of aromatic ring); $^{13}\text{C}(\text{CDCl}_3)$: δ 14.80 (s, OCH_2CH_3); 23.60-24.24 (m, (CH_3) $_2\text{CHOx2}$), 55.89 (s, OCH_3), 64.11 (s, OCH_2CH_3), 70.73 (d, P- CH , $^1J_{\text{PC}}$ 162.97), 71.39-71.82 (m, (CH_3) $_2\text{CHOx2}$), 110.78 (s, C_5 of aromatic ring), 111.94 (d, C_6 of aromatic ring, $^3J_{\text{PCCC}}$ 4.99), 119.94 (d, C_2 of aromatic ring, $^3J_{\text{PCCC}}$ 7.02), 129.53 (s, C_1 of aromatic ring), 147.88 (s, C_3 of aromatic ring), 148.86 (s, C_4 of aromatic ring), 148.86 (s, C_4 of aromatic ring); $^{31}\text{P}(\text{CDCl}_3)$: δ 20.92 (s); FABMS(3-NOBA): $m/z(\%)$ 347 ($[\text{M}+\text{H}]^+$, 16.47), 181 ($[\text{M}+\text{H} - (\text{iPrO})_2\text{P}(\text{O})\text{H}]^+$, 100).

O,O-Diisopropyl α -hydroxy 4-ethoxybenzylphosphonate: C₁₅H₂₅O₅P Found C- 59.47, H- 7.95% C₁₅H₂₅O₅P requires C- 59.95, H- 7.91%; ¹H(CDCl₃): δ 1.12-1.28 (m, 12H, (CH₃)₂CHOx2), 1.41 (t, 3H, OCH₂CH₃, ³J_{HCH} 7.03), 4.03 (q, 2H, OCH₂CH₃, ³J_{HCH} 6.98), 4.19 (m, 1H, OH), 4.55-4.68 (m, 2H, (CH₃)₂CHOx2), 4.87 (m, 1H, P-CH), 6.86 (d, 2H, H_{ortho} of aromatic ring, ³J_{HCH} 8.65), 7.38 (d, 2H, H_{meta} of aromatic ring, ³J_{HCH} 8.74); ¹³C(CDCl₃): δ 23.58-24.22 (m, (CH₃)₂CHOx2), 63.39 (s, OCH₂CH₃), 70.66 (d, P-CH, ¹J_{PC} 162.23), 71.50 (d, (CH₃)₂CHO, ²J_{POC} 7.56), 71.83 (d, (CH₃)₂CHO, ²J_{POC} 7.41), 114.09 (s, C_{ortho} of aromatic ring), 114.11 (s, C_{ortho} of aromatic ring), 128.61 (s, C_{meta} of aromatic ring), 128.67 (s, C_{meta} of aromatic ring), 128.78 (s, C₁ of aromatic ring), 158.71 (s, C₄ of aromatic ring); ³¹P(CDCl₃): δ 20.83 (s); FABMS(3-NOBA): m/z(%) 317 ([M+H]⁺, 20.88), 151 ([M+H - (iPrO)₂P(O)H]⁺, 100).

O,O-Diethyl α -hydroxy 2,3,4-trimethoxybenzylphosphonate: C₁₄H₂₃O₇P Found C- 50.06, H- 6.80%; C₁₄H₂₃O₇P requires C- 50.30, H- 6.89%; ¹H(CDCl₃): δ 1.20 (t, 3H, CH₃CH₂O, ³J_{HCH} 7.07), 1.32 (t, 3H, CH₃CH₂O, ³J_{HCH} 7.07), 3.85 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 4.03-4.20 (m, 4H, CH₃CH₂Ox2), 4.37 (t, 1H, P-CHOH, ³J_{HCH} 7.41), 5.29-5.34 (m, 1H, P-CHOH), 6.71 (d, 1H, H₅ of aromatic ring, ³J_{HCH} 8.77), 7.29 (dd, 1H, H₆ of aromatic ring, ³J_{HCH} 8.70); ¹³C(CDCl₃): δ 16.42 (dd, CH₃CH₂Ox2, ³J_{POCC} 5.72), 55.96 (s, CH₃O), 60.67 (s, CH₃O), 61.35 (s, CH₃O), 62.97 (dd, CH₃CH₂Ox2, ²J_{POC} 6.91), 65.20 (d, P-CH, ¹J_{PC} 163.75); ³¹P(CDCl₃): δ 22.93 (s); FABMS(3-NOBA): m/z(%) 335 ([M+H]⁺, 25.00), 197 ([M+H - (EtO)₂P(O)H]⁺, 100).

General method for preparation of *O,O*-dialkyl α -bromobenzylphosphonates

O,O-Dialkyl α -hydroxybenzylphosphonate (0.01 mol) and CDI (0.01 mol) were dissolved in anhydrous MeCN (25 cm³), treated with allyl bromide (5 mol eq) and stirred vigorously for 30 min at R.T. The clear solution was then heated under reflux for 4h at 150°C. After cooling, ether (70 cm³) and H₂O (30 cm³) was added to the solution. The organic layer was washed with 1M HCl, 1M NaHCO₃ and H₂O, before being dried over MgSO₄. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure to afford an oily residue. A solution of this material in hexane (50 cm³) was treated with SiO₂ (1g) and then evaporated under reduced pressure to afford a colorless oily residue in quantitative yield. Analytical data is given below for a few of the examples prepared.

O,O-Diethyl α -bromo 4-ethoxybenzylphosphonate: C₁₃H₂₀O₄PBr Found C- 44.34, H- 5.29%; C₁₃H₂₀O₄PBr requires C-44.44, H- 5.70%; ¹H(CDCl₃): δ 1.15 (t, 3H, OCH₂CH₃, ³J_{HCH} 7.00), 1.34 (t, 3H, CH₃CH₂O, ³J_{HCH} 7.12), 1.40 (t, 3H, CH₃CH₂O, ³J_{HCH} 6.94), 4.00-4.27 (m, 6H, OCH₂CH₃, CH₃CH₂Ox2), 4.86 (d, 1H, P-CH, ²J_{PCH} 12.73), 6.85 (d, 2H, ortho H's, ³J_{HCH} 8.73), 7.49 (d, 2H, meta H's, ³J_{HCH} 8.67); ¹³C(CDCl₃): δ 14.75 (s,

OCH_2CH_3), 16.25 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{POCC}}$ 5.81), 16.43 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{POCC}}$ 5.85), 41.57 (d, P-CH , $^1J_{\text{PC}}$ 162.00), 63.50 (s, OCH_2CH_3), 63.97 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^2J_{\text{POC}}$ 6.54), 64.04 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^2J_{\text{POC}}$ 6.63), 114.59 (s, C_{meta}), 126.32 (d, C_1 of aromatic ring, $^2J_{\text{PCC}}$ 3.09), 130.85 (s, C_{ortho}), 159.48 (s, C_4 of aromatic ring); $^{31}\text{P}(\text{CDCl}_3)$: δ 17.89 (s); FABMS(3-NOBA): $m/z(\%)$ 375 ($[\text{M}+\text{H}+\text{Na}]^+$, 62.0), 271 ($[\text{M}+\text{H}-\text{HBr}]^+$, 100).

O,O-Diethyl α -bromo 2,3,4-trimethoxybenzylphosphonate: $\text{C}_{14}\text{H}_{22}\text{O}_6\text{PBr}$ requires C- 42.32, H- 5.41%; $^1\text{H}(\text{CDCl}_3)$: δ 1.18 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HCCCH}}$ 7.07), 1.36 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{HCCCH}}$ 7.12), 3.86 (s, 3H, $\text{C}_3\text{-OCH}_3$), 3.87 (s, 3H, $\text{C}_2\text{-OCH}_3$), 3.95 (s, 3H, $\text{C}_4\text{-OCH}_3$), 4.05-4.31 (m, 4H, $\text{CH}_3\text{CH}_2\text{O} \times 2$), 5.49 (d, 1H, P-CH , $^2J_{\text{PCH}}$ 12.72), 6.73 (d, 1H, H_5 of aromatic ring, $^3J_{\text{HCCCH}}$ 8.92), 7.58-7.62 (m, 1H, H_6 of aromatic ring); $^{13}\text{C}(\text{CDCl}_3)$: δ 16.27 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{POCC}}$ 5.76), 16.45 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^3J_{\text{POCC}}$ 6.01), 33.90 (d, P-CH , $^1J_{\text{PC}}$ 165.49), 55.99 (s, $\text{C}_3\text{-OCH}_3$), 60.82 (s, $\text{C}_2\text{-OCH}_3$), 61.35 (s, $\text{C}_4\text{-OCH}_3$), 63.82 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^2J_{\text{POC}}$ 7.09), 64.08 (d, $\text{CH}_3\text{CH}_2\text{O}$, $^2J_{\text{POC}}$ 6.98), 107.94 (s, C_5 of aromatic ring), 125.94 (d, C_6 of aromatic ring, $^3J_{\text{PCCC}}$ 3.78), 120.91 (s, $\text{C}_3\text{-OCH}_3$), 141.65 (s, $\text{C}_2\text{-OCH}_3$), 151.42 (d, C_1 of aromatic ring, $^2J_{\text{PCC}}$ 8.64), 154.33 (s, $\text{C}_4\text{-OCH}_3$); $^{31}\text{P}(\text{CDCl}_3)$: δ 18.49 (s); FABMS(3-NOBA): $m/z(\%)$ 398 ($[\text{M}+\text{H}]^+$, 9.17), 317 ($[\text{M}+\text{H}-\text{HBr}]^+$, 100).

O,O-Di-*n*-butyl α -bromo 4-methoxybenzylphosphonate: $\text{C}_{16}\text{H}_{26}\text{O}_4\text{PBr}$ requires C- 48.86, H- 6.62%; $^1\text{H}(\text{CDCl}_3)$: δ 0.84 (t, 3H, terminal CH_3 , $^3J_{\text{HCCCH}}$ 7.38), 0.93 (t, 3H, terminal CH_3 , $^3J_{\text{HCCCH}}$ 7.39), 1.21-1.69 (m, 8H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O} \times 2$), 3.80 (s, 3H, OCH_3), 3.94-4.18 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O} \times 2$), 4.87 (d, 1H, P-CH , $^2J_{\text{PCH}}$ 12.74), 6.86 (d, 2H, H_{ortho} , $^3J_{\text{HCCCH}}$ 8.64), 7.50 (dd, 2H, H_{meta} , $^3J_{\text{HCCCH}}$ 8.68); $^{13}\text{C}(\text{CDCl}_3)$: δ 13.51 (s, terminal CH_3), 13.58 (s, terminal CH_3), 18.55 (s, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 18.66 (s, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 32.40 (d, $\text{CH}_2\text{CH}_2\text{O}$, $^3J_{\text{POCC}}$ 5.70), 32.56 (d, $\text{CH}_2\text{CH}_2\text{O}$, $^3J_{\text{POCC}}$ 5.80), 41.51 (d, P-CH , $^1J_{\text{PC}}$ 162.18), 55.32 (s, CH_3O), 67.62 (d, CH_2O , $^2J_{\text{POC}}$ 7.44), 67.69 (d, CH_2O , $^2J_{\text{POC}}$ 7.53), 114.12 (s, C_{meta}), 130.88 (s, C_{ortho}), 126.75 (d, C_1 of aromatic ring, $^2J_{\text{PCC}}$ 3.24), 160.11 (s, $\text{C}_4\text{-OCH}_3$); $^{31}\text{P}(\text{CDCl}_3)$: δ 17.77 (s); FABMS(3-NOBA): $m/z(\%)$ 394 ($[\text{M}+\text{H}]^+$, 4.45), 313 ($[\text{M}+\text{H}-\text{HBr}]^+$, 92.65).

O,O-Diisopropyl α -bromo 3-ethoxy, 4-methoxybenzylphosphonate: $\text{C}_{16}\text{H}_{26}\text{O}_5\text{PBr}$ requires C- 46.94, H- 6.36%; $^1\text{H}(\text{CDCl}_3)$: δ 1.25-1.38 (m, 12H, $(\text{CH}_3)_2\text{CHO} \times 2$), 1.47 (t, 3H, OCH_2CH_3 , $^3J_{\text{HCCCH}}$ 6.98), 3.87 (s, 3H, OCH_3), 4.14 (q, 2H, OCH_2CH_3 , $^3J_{\text{HCCCH}}$ 6.95), 4.49-4.57 (m, 1H, $(\text{CH}_3)_2\text{CHO}$), 4.79 (d, 1H, P-CH , $^2J_{\text{PCH}}$ 12.82), 4.82-4.88 (m, 1H, $(\text{CH}_3)_2\text{CHO}$), 6.79 (d, 1H, H_5 of aromatic ring, $^3J_{\text{HCCCH}}$ 8.30), 7.02 (d, 1H, H_6 of aromatic ring), 7.25 (s, 1H, H_2 of aromatic ring); $^{13}\text{C}(\text{CDCl}_3)$: δ 14.64 (s, OCH_2CH_3), 23.20-24.30 (m, $(\text{CH}_3)_2\text{CHO} \times 2$), 42.62 (d, P-CH , $^1J_{\text{PC}}$ 163.87), 55.90 (s, OCH_3), 64.28 (s, OCH_2CH_3), 72.63 (d, $(\text{CH}_3)_2\text{CHO}$, $^2J_{\text{POC}}$ 6.74), 72.69 (d, $(\text{CH}_3)_2\text{CHO}$, $^2J_{\text{POC}}$ 5.99), 110.76 (s, C_5 of aromatic ring), 113.73 (s, C_6 of aromatic ring), 122.19 (s, C_2 of aromatic ring), 127.18 (d, C_1 of aromatic ring, $^2J_{\text{PCC}}$

2.61), 148.18 (s, C₄-OCH₃), 149.83 (s, C₃-OCH₂CH₃); ³¹P(CDCl₃): δ 16.34 (s); FABMS(3-NOBA): m/z(%) 410 ([M+H]⁺, 13.67), 329 ([M+H-HBr]⁺, 50.0).

O,O-Diisopropyl α-bromo 4-ethoxybenzylphosphonate: C₁₅H₂₄O₄PBr Found C- 47.21, H- 6.06%; C₁₅H₂₄O₄PBr requires C- 47.49, H- 6.33%; ¹H(CDCl₃): δ 1.25-1.42 (m, 15H, (CH₃)₂CHOx2 overlapping OCH₂CH₃), 3.99-4.05 (m, 2H, OCH₂CH₃), 4.49-4.61 (m, 1H, (CH₃)₂CHO), 4.82 (d, 1H, P-CH, ²J_{PCH} 12.92), 4.79-4.86 (m, 1H, (CH₃)₂CHO), 6.84 (d, 2H, H_{ortho}, ³J_{HCH} 8.20), 7.49 (d, 2H, H_{meta}, ³J_{HCH} 8.64); ¹³C(CDCl₃): δ 14.74 (s, OCH₂CH₃), 23.16-24.28 (m, (CH₃)₂CHOx2), 42.28 (d, P-CH, ¹J_{PC} 163.51), 63.46 (s, OCH₂CH₃), 72.50 (d, (CH₃)₂CHO, ²J_{POC} 7.35), 72.64 (d, (CH₃)₂CHO, ²J_{POC} 6.93), 114.47 (s, C_{meta} of aromatic ring), 126.74 (d, P-CHC₁, ²J_{PCC} 2.71), 130.95 (s, C_{ortho} of aromatic ring), 159.38 (s, C₄-OCH₂CH₃); ³¹P(CDCl₃): δ 16.28 (s); FABMS(3-NOBA): m/z(%) 380 ([M+H]⁺, 1.94), 299 ([M+H-HBr]⁺, 47.90).

General method for preparation of *O,O*-dialkyl α-iodobenzylphosphonates

O,O-Dialkyl α-hydroxybenzylphosphonate (0.01 mol) and CDI (0.01 mol) were dissolved in anhydrous MeCN (25 cm³), treated with methyl iodide (5 mol eq) and stirred vigorously for 30 min at R.T. The clear solution was heated under reflux for 4h at 150°C. After cooling, ether (70 cm³) and H₂O (30 cm³) were added to the solution. The organic layer was washed with 1M HCl, 1M NaHCO₃, 10% aq Na₂S₂O₃ and H₂O, before being dried over MgSO₄. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure to afford an oily reddish brown residue. A solution of this material in hexane (50 cm³) was treated with SiO₂ (1g) and then evaporated under reduced pressure to afford a reddish-brown oily residue in quantitative yield. Analytical data is given below for a few of the examples prepared.

O,O-Diisopropyl α-iodo 2,3,4-trimethoxybenzylphosphonate: C₁₆H₂₆O₆PI Found C-40.40, H- 5.15%; C₁₆H₂₆O₆PI requires C-40.68, H- 5.51%; ¹H(CDCl₃): δ 1.23-1.39 (m, 12H, (CH₃)₂CHOx2), 3.89 (s, 3H, C₂-OCH₃), 3.96 (s, 3H, C₃-OCH₃), 4.03 (s, 3H, C₄-OCH₃), 4.49-4.84 (m, 2H, (CH₃)₂CHOx2), 5.59 (d, 1H, P-CH, ²J_{PCH} 13.23), 6.69 (d, 1H, H₆ of aromatic ring, ³J_{HCH} 9.00), 7.60 (d, 1H, H₅ of aromatic ring, ³J_{HCH} 8.72); ¹³C(CDCl₃): δ 16.50 (d, P-CH, ¹J_{PC} 160.20), 23.28-24.20 (m, (CH₃)₂CHOx2), 56.02 (s, C₃-OCH₃), 56.28 (s, C₂-OCH₃), 60.84 (s, C₄-OCH₃), 72.57 (d, (CH₃)₂CHO, ²J_{POC} 7.53), 72.76 (d, (CH₃)₂CHO, ²J_{POC} 7.32); ³¹P(CDCl₃): δ 18.44 (s); FABMS(3-NOBA): m/z(%) 473 ([M+H]⁺, 2.78), 345 ([M+H-HI]⁺, 100).

O,O-Diethyl α-iodo 4-ethoxybenzylphosphonate: C₁₃H₂₀O₄PI Found C- 39.61, H- 4.82%; C₁₃H₂₀O₄PI requires C- 39.20, H- 5.03%; ¹H(CDCl₃): δ 1.14 (t, 3H, OCH₂CH₃, ³J_{HCH} 7.14), 1.33 (t, 3H, CH₃CH₂O, ³J_{HCH} 7.12), 1.40 (t, 3H, CH₃CH₂O, ³J_{HCH} 7.05), 4.01 (m, 2H, OCH₂CH₃, ³J_{HCH} 7.07), 4.03-4.26 (m, 4H, CH₃CH₂Ox2), 5.00

(d, 1H, P-CH, $^2J_{\text{PCH}}$ 13.22), 6.81 (d, 2H, H_{ortho}, $^3J_{\text{HCCH}}$ 8.63), 7.49 (d, 2H, H_{meta}, $^3J_{\text{HCCH}}$ 7.07); $^{13}\text{C}(\text{CDCl}_3)$: δ 14.76 (s, OCH₂CH₃), 15.43 (d, P-CH, $^1J_{\text{PC}}$ 158.44), 16.24 (d, CH₃CH₂O, $^3J_{\text{POCC}}$ 7.03), 16.39 (d, CH₃CH₂O, $^3J_{\text{POCC}}$ 6.08), 63.50 (s, OCH₂CH₃), 64.05 (d, CH₃CH₂O, $^2J_{\text{POC}}$ 6.95), 64.20 (d, CH₃CH₂O, $^2J_{\text{POC}}$ 7.14), 114.67 (s, C_{meta}), 127.86 (d, C₁ of aromatic ring, $^2J_{\text{PCC}}$ 3.38), 130.80 (s, C_{ortho} of aromatic ring), 150.07 (s, C₄-OCH₂CH₃); $^{31}\text{P}(\text{CDCl}_3)$: δ 19.57 (s); FABMS(3-NOBA): m/z (%) 399 ([M+H]⁺, 15.56), 271 ([M+H-HI]⁺, 100).

O,O-Diisopropyl α -iodo 4-ethoxybenzylphosphonate: C₁₅H₂₄O₄PI requires C- 42.65, H- 5.23%; $^1\text{H}(\text{CDCl}_3)$: δ 1.23-1.47 (m, 15H, (CH₃)₂CHOx2 overlapping OCH₂CH₃), 4.01 (m, 2H, OCH₂CH₃, $^3J_{\text{HCCH}}$ 6.90), 4.50-4.91 (m, 2H, (CH₃)₂CHOx2), 4.94 (d, 1H, P-CH, $^2J_{\text{PCH}}$ 13.32), 6.80 (d, 2H, H_{ortho} of aromatic ring, $^3J_{\text{HCCH}}$ 8.70), 7.49 (d, 2H, H_{meta} of aromatic ring, $^3J_{\text{HCCH}}$ 8.71); $^{13}\text{C}(\text{CDCl}_3)$: δ 14.75 (s, OCH₂CH₃), 16.80 (d, P-CH, $^1J_{\text{PC}}$ 160.14), 23.13-24.26 (m, (CH₃)₂CHOx2), 63.48 (s, OCH₂CH₃), 71.45-72.81 (m, (CH₃)₂CHOx2), 114.57 (s, C_{meta}), 128.47 (d, C₁ of aromatic ring, $^2J_{\text{PCC}}$ 2.88), 130.85 (s, C_{ortho} of aromatic ring), 158.96 (s, C₄-OCH₂CH₃); $^{31}\text{P}(\text{CDCl}_3)$: δ 18.02 (s); FABMS(3-NOBA): m/z (%) 875 ([2M+Na]⁺, 10.0), 449 ([M+Na]⁺, 82.94).

O,O-Di-*n*-butyl α -iodo 4-methoxybenzylphosphonate: C₁₆H₂₆O₄PI requires C- 43.64, H- 5.91%; $^1\text{H}(\text{CDCl}_3)$: δ 0.83 (t, 3H, terminal CH₃, $^3J_{\text{HCCH}}$ 7.38), 0.93 (t, 3H, terminal CH₃, $^3J_{\text{HCCH}}$ 7.40), 1.20-1.69 (m, 8H, CH₃CH₂CH₂CH₂Ox2), 3.79 (s, 3H, OCH₃), 3.82-4.17 (m, 4H, CH₂Ox2), 5.01 (d, 1H, P-CH, $^2J_{\text{PCH}}$ 13.19), 6.82 (d, 2H, H_{meta} of aromatic ring, $^3J_{\text{HCCH}}$ 8.71), 7.51 (d, 2H, H_{ortho} of aromatic ring, $^3J_{\text{HCCH}}$ 8.65); $^{13}\text{C}(\text{CDCl}_3)$: δ 13.53 (s, terminal CH₃), 13.60 (s, terminal CH₃), 15.30 (d, P-CH, $^1J_{\text{PC}}$ 158.36), 18.53 (s, CH₃CH₂CH₂CH₂O), 18.66 (s, CH₃CH₂CH₂CH₂O), 32.37 (d, CH₃CH₂CH₂CH₂O, $^3J_{\text{POCC}}$ 5.90), 32.48 (s, CH₃CH₂CH₂CH₂O, $^3J_{\text{POCC}}$ 5.90), 55.30 (s, OCH₃), 67.57 (d, CH₂O, $^2J_{\text{POC}}$ 7.51), 67.74 (d, CH₂O, $^2J_{\text{POC}}$ 7.00), 114.14 (s, C_{meta} of aromatic ring), 128.32 (d, PCHC₁, $^2J_{\text{PCC}}$ 3.52), 130.80 (s, C_{ortho} of aromatic ring), 159.64 (s, C₄-OCH₃); $^{31}\text{P}(\text{CDCl}_3)$: δ 19.45 (s); FABMS(3-NOBA): m/z (%) 463([M+Na]⁺, 12.06).

O,O-Diisopropyl α -iodo 3-ethoxy, 4-methoxybenzylphosphonate: C₁₆H₂₆O₅PI requires C- 42.11, H- 5.70%; $^1\text{H}(\text{CDCl}_3)$: δ 1.23-1.51 (m, 15H, (CH₃)₂CHOx2 overlapping OCH₂CH₃), 3.86 (s, 3H, OCH₃), 4.17 (m, 2H, OCH₂CH₃, $^3J_{\text{HCCH}}$ 7.01), 4.49-4.91 (m, 2H, (CH₃)₂CHOx2), 4.95 (d, 1H, P-CH, $^2J_{\text{PCH}}$ 13.12), 6.75 (d, 1H, H₆ of aromatic ring, $^3J_{\text{HCCH}}$ 8.34), 6.99 (d, 1H, H₅ of aromatic ring, $^3J_{\text{HCCH}}$ 8.18), 7.23 (s, 1H, H₂ of aromatic ring); $^{13}\text{C}(\text{CDCl}_3)$: δ 14.63 (s, OCH₂CH₃), 17.03 (d, P-CH, $^1J_{\text{PC}}$ 160.20), 23.68-24.35 (m, (CH₃)₂CHOx2), 55.92 (s, OCH₃), 64.31 (s, OCH₂CH₃), 72.73 (d, (CH₃)₂CHO, $^2J_{\text{POC}}$ 7.48), 73.06 (d, (CH₃)₂CHO, $^2J_{\text{POC}}$ 6.98), 110.57 (s, C₅ of aromatic ring), 114.00 (s, C₆ of aromatic ring), 119.97 (d, P-C-C₁, $^2J_{\text{PCC}}$), 121.79 (s, C₂ of aromatic ring), 148.88 (s, C₃ of aromatic ring), 154.72 (s, C₄ of

aromatic ring); $^{31}\text{P}(\text{CDCl}_3)$: δ 17.94 (s); FABMS(3-NOBA): $m/z(\%)$ 457 ($[\text{M}+\text{H}]^+$, 8.34), 330 ($[\text{M}+\text{H}-\text{HI}]^+$, 38.67).

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