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Synthesis and anti-parasitic activity of *C*-benzylated (*N*-arylcarbamoyl)alkylphosphonate esters

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ABSTRACT

Unexpected substituent-dependent regioselectivty challenges in the synthesis of *C*-benzylated (*N*-arylcarbamoyl)phosphonate esters have been resolved. The *C*-benzylated *N*-furfurylcarbamoyl derivative showed low micromolar *Pf*LDH inhibition, while one of the *C*-benzylated *N*-arylcarbamoyl analogues was active against Nagana *Trypanosoma brucei* parasites which are responsible for African trypanosomiasis in cattle.

1. Introduction

Malaria remains a major international health concern, particularly in developing countries,[1] and the identification of new targets for therapeutic intervention provides opportunities for discovering new antimalarial agents. The *Plasmodium falciparum* enzyme, 1-deoxy-1-D-xylulose-5-phosphate reductoisomerase (*Pf*DXR), has been identified as such a target.[2] Fosmidomycin **1**, a naturally occurring antibiotic, and its acetyl analogue FR900098 **2** are known to inhibit this enzyme[3] and, in our research programme, we have been investigating various 'reverse' fosmidomycin analogues **3** as potential *Pf*DXR inhibitors (Fig. 1).

In silico examination of the intramolecular topology of the *Pf*DXR active-site[4] has confirmed the presence of nearby hydrophobic pockets, and *N*-benzylated phosphonate ester analogues, containing a bimethylene spacer between the phosphonate and amide moieties, have been prepared from *N*-benzylated arylamines in the expectation that the hydrophobic benzyl moiety would occupy such a pocket.[5,6] Surprisingly, while a number of these compounds exhibited activity against the *Pf* parasite ($IC_{50} \geq 10.12$ μM), they were inactive (as their phosphonic acid derivatives) against the *Pf*DXR enzyme, thus suggesting the involvement of a different but, as yet, unknown mechanism. In this communication we report the preparation of the series of *C*-benzylated analogues (**6**) in which the phosphonate and amide moieties are separated by a single methylene spacer (Schemes 1 and 3).

2. Results and discussion

Access to the desired *C*-benzylated phosphonate esters (**6**) proved unexpectedly frustrating. Direct, base-catalysed benzylation of the (*N*-arylcarbamoyl)phosphonate esters **5a-f**, which we had synthesised previously,[4] was considered a reasonable option, and exploratory studies were undertaken using the available furfurylamine-derived phosphonate ester **5a** as the substrate. Five different methods (***A-E***; Scheme 1) were investigated. Reactions in dry THF using pyridine (*method* ***A***) or triethylamine (*method* ***B***) as the base, both at room temperature and at reflux, failed to afford any of the desired product. Refluxing a mixture of the phosphonate ester **5a** with benzyl bromide in 10% aqueous NaOH for *ca* 2 h (*method* ***C***) was similarly unsuccessful. Use of finely powdered KOH in dry THF (*method* ***D***) afforded the desired *C*-benzylated

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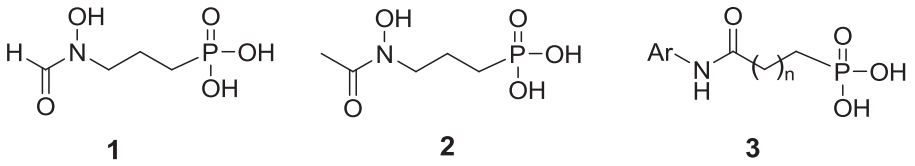
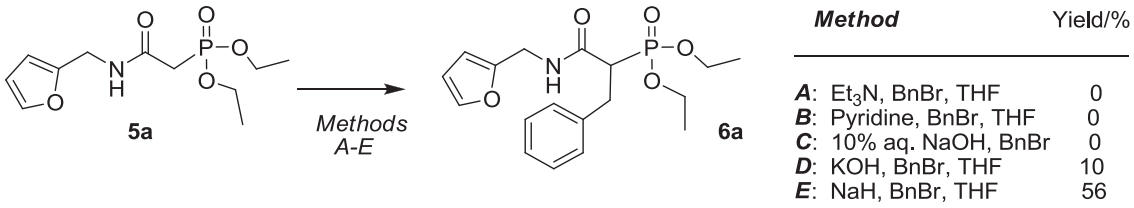


Fig. 1. Structures of the *Pf*DXR inhibitor fosmidomycin **1**, its acetyl analogue FR900098 **2** and 'reverse' fosmidomycin analogues **3**.

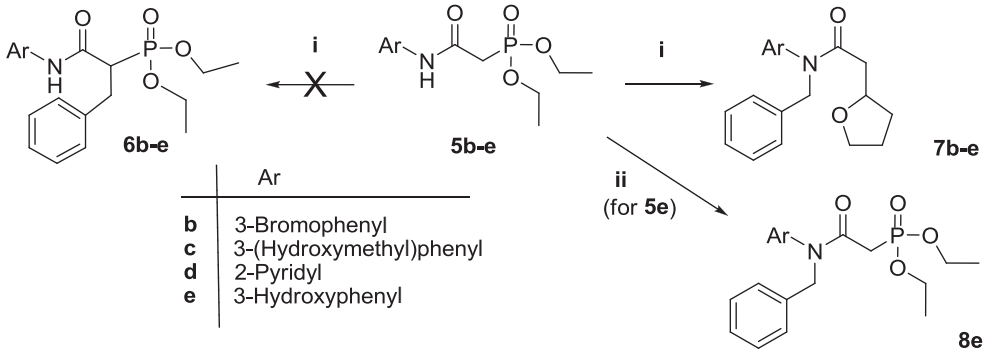


Scheme 1. Approaches to the preparation of compound **6a**.

phosphonate ester **6a**, but only in 10% yield. The benzylation of *N*-arylcarboxamides under various conditions appears to favour the *N*-benzylated products – as reflected in the reaction of *N*-arylacetamides with benzyl bromide and NaH in THF as reported by Clarke et al.[7] However, reaction of the (*N*-furfurylcarbamoyl)phosphonate ester **5a** under similar conditions (*method **E***) gave a very different result. Thus, a solution of the phosphonate ester **5a** in dry THF was boiled under reflux with sodium hydride as base for *ca* 6 h and benzyl bromide (2.4 equivalents) was then added in two portions. After refluxing the mixture for 4 h, work-up and chromatography afforded the *desired C*-benzylated phosphonate ester **6a** in 56% yield – *not* the *N*-benzylated analogue! *C*-Benzylation is clearly supported by the NMR data. Thus, a *P*-methine proton multiplet at δ 3.03 ppm in the ^{1}H NMR spectrum of the product **6a**, replaces the *P*-methylene proton doublet at δ 2.87 ppm observed in the spectrum of the precursor **5a**, while DEPT-135 NMR spectra show a *P*-methylene doublet for **5a** at δ 34.2 ppm and a *P*-methine doublet for **6a** at δ 47.1 ppm.[8]

Given its successful use in the α-benzylation of the furfurylamine-derived phosphonate ester **5**a, *method **E*** (involving reaction with benzyl bromide in dry THF in the presence of NaH) was applied to the (*N*-arylcarbamoyl)phosphonate esters **5b-e**. However, ^{1}H NMR analysis of each of the purified products revealed the absence of the phosphonate ester moiety. Careful examination of the experimental data revealed that a totally unexpected transformation had taken place to form the *N*-benzylated tetrahydrofuran-2-yl derivatives **7b-e** (Scheme 2). The origin of the tetrahydrofuran-2-yl moiety is attributed to the presence of the cyclic enol ether, 2,3-dihydrofuran, in the batch of THF used as the solvent in these reactions.[8] Repetition of the reaction with compound **5e** using fresh THF, however, simply afforded the *N*-benzylated product **8e** rather than the desired *C*-benzylated analogues – and not the unusual tetrahydrofuran-2-yl derivative **7e**.[8] It seems that the presence of the furfuryl group in compound **5a** *decreases the acidity* of the amide proton sufficiently,[9] relative to the methylene protons adjacent to the carbonyl group, to permit formation of the enolate **I** (Fig. 2) and subsequent *C*-benzylation to afford compound **6a**. However, in compound **5e** (and, presumably, in the *N*-arylacetamides discussed by Clarke et al.[7]) the electron-withdrawing *N*-aryl group *enhances the acidity* of the amide proton sufficiently (*via* both - I and - M effects) to facilitate formation of the resonance-stabilised anion **II** and, hence, the *N*-benzylation observed in this case and elsewhere.[7]

Clearly, while the furfuryl derivative **6a** could be obtained using *method **E*** (Scheme 1), alternative approaches to an expanded series of the desired *C*-benzylated (*N*-arylcarbamoyl)phosphonate esters had to be explored. 2-Bromo-3-phenylpropanoic acid **11** was identified as a possible key intermediate in the construction of the remaining targeted compounds (**6**) (Scheme 3). Catalytic hydrogenation of cinnamic acid **9** afforded 3-phenylpropanoic acid **10**, but attempted α-bromination of the latter compound using the Hell-Volhard-Zelinsky reaction[10] failed to afford compound **11**. Attention was consequently turned to the preparation of the α-chloro analogue **14** instead. *N*-Boc-phenylalanine **12** was deprotected by stirring with 4M-HCl in dioxane for 2 h at room temperature; work-up and trituration with EtOAc afforded phenylalanine hydrochloride **13** in yields of up to 96%. Diazotisation of the phenylalanine salt **13** in 6M-HCl afforded 2-chloro-3-



Scheme 2. Unsuccessful attempts to effect C-benzylation of the carbamoylphosphonate esters **5b-e**. *Reagents and conditions*: i) NaH, BnBr, THF; ii) NaH, BnBr, fresh THF.

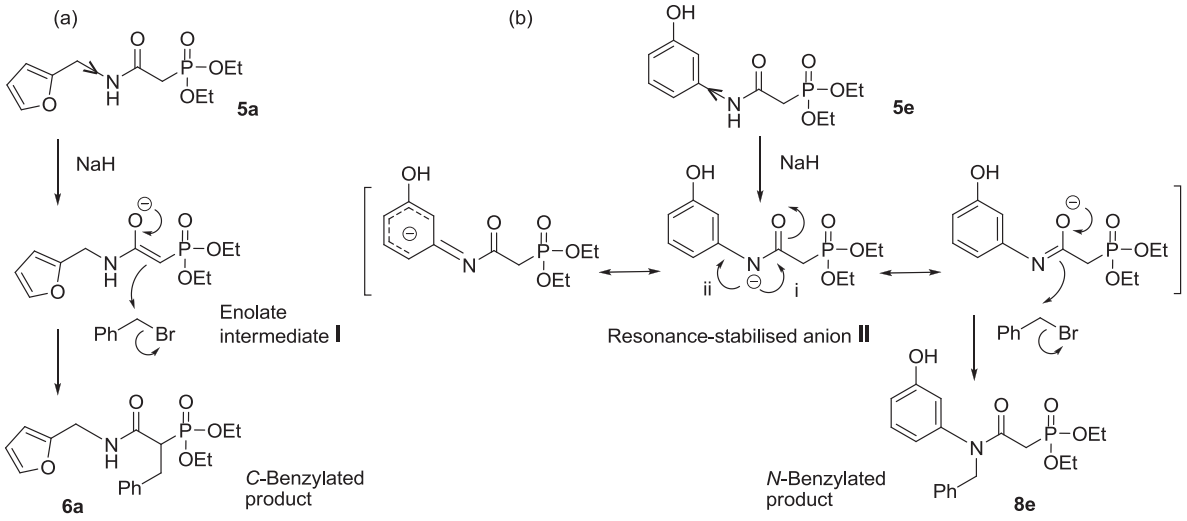
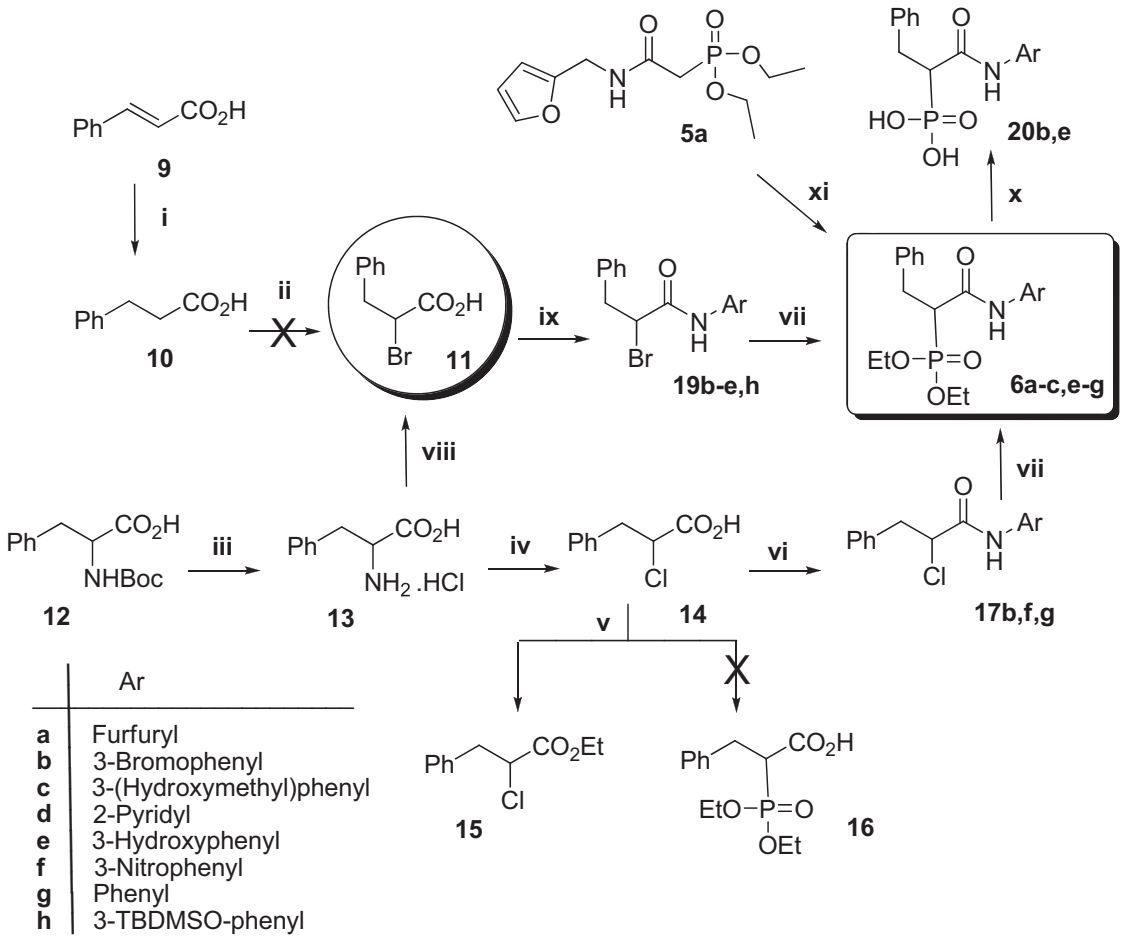


Fig. 2. a) *C*-Benzylation of the *N*-furfuryl derivative **5a**. b) *N*-Benzylation of the *N*-(3-hydroxyphenyl) derivative **5e**.



Scheme 3. Synthetic routes to the carbamoylphosphonate esters (**6**).*Reagents and conditions:*- (i) H_2, 10% Pd/C catalyst, AcOH; (ii) PBr_3; (iii) 4M-HCl, dioxane, r.t., 2 h; (iv) 6M-HCl, $NaNO_2$, H_2O, r.t., 24 h; (v) triethyl phosphite, 120–150 °C, 5 h; (vi) $SOCl_2$, DMF, 70 °C, 1 h, *then* $ArNH_2$, DMF, overnight.; (vii) triethyl phosphite, 120–150 °C, 10 h; (viii) NaBr, $NaNO_2$, 4M-H_2SO_4, H_2O, r.t.; (ix) CDI, DCM, $ArNH_2$; (x) TMSBr, DCM; (xi) NaH, BnBr, THF.

phenylpropanoic acid **14**[11] which, on reaction with triethyl phosphite, gave the corresponding ethyl ester **15** instead of the expected phosphonate ester **16**. Consequently, amidation of 2-chloro-3-phenylpropanoic acid **14** was effected *via* the acid chloride which was reacted directly with the aromatic amines, aniline and 3-bromoaniline. Work-up and flash-chromatography afforded the corresponding, *N*-aryl-2-chloro-3-phenylpropanamides **17g** (which is known[12]), **17b** and **17f** in moderate yields (65–71%). Michaelis-Arbuzov reactions of the intermediates **17f** and **17g** in refluxing triethyl phosphite (3 eq.) led to the targeted *C*-benzylated

(*N*-arylcarbamoyl)phosphonate esters **6f** and **6g**, but in low yields (25–45%).

Since bromide is generally a better leaving group than chloride, attention returned to the use of 2-bromo-3-phenylpropanoic acid **11** in place of the 2-chloro analogue **14**. In a variation of the diazotisation conditions, a solution of phenylalanine hydrochloride **13** in 4M-H_2SO_4 (in place of 6M-HCl) was treated with NaBr (3.5 eq) and $NaNO_2$ (1.25 eq) in water at 0 °C to produce 2-bromo-3-phenylpropanoic acid **11** in 72% yield.[13] The *N*-substituted 2-bromopropanamides **19b-e,h** were then obtained in 60–65% yield by reacting the corresponding aromatic amines with 2-bromo-3-phenylpropanoic acid **11** in the presence of the coupling agent 1,1'-carbonyldiimidazole (CDI) in DCM[14] (instead of using the acid chloride used to access to the 2-chloropropanamide analogues). Similar reaction of 3-(hydroxymethyl)aniline, however, afforded the *N*,*O*-diacylated analogue, necessitating protection of the hydroxyl group prior to amidation. This was achieved by reacting 3-(hydroxymethyl)aniline with *tert*-butyldimethylsilyl chloride (TBDMSCl; 1.1 eq) and imidazole (1.5 eq) at 0 °C in dry DCM, and the resulting TBDMS ether-protected derivative **18** was reacted with CDI and 2-bromo-3-phenylpropanoic acid **11** to afford (following *in situ* cleavage of the unstable silyl ether **19h**) 2-bromo-*N*-(hydroxymethyl)-2-phenylpropanamide **19c**. Arbuzov reactions of the 2-bromo-2-phenylpropanamides with triethyl phosphite finally afforded the phosphonate esters **6b**,**c**,**e** in moderate yield (32–61%) following chromatography. An interesting feature of the ^{13}C NMR spectra of the *chiral C*-benzylated phosphonate esters (**6**) is that the inherently *diastereotopic* phosphonate *O*-methylene carbons are observed to resonate as a *pair* of doublets exhibiting, in some cases, slightly different $J_{P,C}$ values.

Thus, while the furfuryl derivative **6a** was readily obtained *via* direct *N*-benzylation of the phosphonate ester precursor **5a** (Scheme 1), the *N*-aryl analogues **6b,c,e-g** had to be accessed by very different routes, commencing from *N*-Boc-phenylalanine **12** (Scheme 3). Although the purified phosphonate esters might have been expected to serve directly as possible pro-drugs in the *P.falciparum* parasite (*Pf*LDH) bioassays, *in vitro* evaluation of specific *Pf*DXR inhibition potential was expected to require the use of the phosphonic acid analogues. The phosphonate ester **6e** was hydrolysed to the corresponding, representative acid **20e** using bromotrimethylsilane in dry DCM.[14] The phosphonic acid and the phosphonate esters were then subjected to screening using a range of *in vitro* bioassays.[15]

None of the compounds tested (**6a-c,e-g** and **20e**) exhibited significant cytotoxicity against HeLa cells in concentrations of up to 100 μM; above this concentration, however, all nine compounds were toxic. The *C*-benzylated (*N*-furfurylcarbamoyl)phosphonate ester **6a** exhibited low micromolar activity against malaria parasite lactate dehydrogenase (*Pf*LDH) (16.1% *Pf*LDH viability at 20 μM; IC_{50} = 16.4 μM). This represents a marked improvement in activity compared to the non-benzylated precursor **5a** (64.1% *Pf*LDH viability at 20 μM). Surprisingly, the *C*-benzylated (*N*-arylcarbamoyl)phosphonate esters **6b**,**c**,**e-g** – unlike the *C*-benzylated (*N*-furfurylcarbamoyl)phosphonate ester **6a** or the *N*-benzylated dimethylene-linked analogues[5] – failed to exhibit any significant *Pf*LDH inhibition. The *C*-benzylated phosphonic acid **20e** also failed to inhibit *Pf*DXR significantly at 20 μM. One of the compounds, however, showed modest activity (**6b**: IC_{50} = 31 μM) against Nagana *Trypanosoma brucei (T.b.)* parasites which are responsible for African trypanosomiasis in cattle – an important agricultural problem.

In conclusion, convenient synthetic routes have been established to access a range of *C*-benzylated diethyl phosphonate derivatives, and implicit regioselectivity issues have been resolved. While the *C*-benzylated *N*-furfurylcarbamoyl derivative **6a** exhibited encouraging anti-malarial activity, the *C*-benzylated *N*-arylcarbamoyl derivatives **6b,c,e-g** exhibited little if any such activity. The observed inhibition of Nagana *Trypanosoma brucei* by one of the *C*-benzylated *N*-arylcarbamoyl derivatives, however, raises interesting possibilities for parallel studies on the development of novel trypanocides.

3. Experimental

^1H and ^{13}C NMR spectra were typically recorded on Bruker 300, 400 or 600 MHz spectrometers in $CDCl_3$ and calibrated using solvent signals [δ_H: 7.26 ppm for residual $CHCl_3$; δ_C: 77.0 ppm ($CDCl_3$)]. Melting points were measured using a hot-stage apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded on a Waters API Q-TOF Ultima spectrometer (University of Stellenbosch, Stellenbosch, South Africa). NMR spectra for new compounds are available in the Supporting Information (File II). Methods for the preparation and characterisation of new compounds are as follows.

3.1. Diethyl 1-(N-furfurylcarbamoyl)-2-phenylethylphosphonate *6a*

A solution of diethyl (furfurylcarbamoyl)methylphosphonate **5a** (0.35 g, 1.3 mmol) in THF (10 mL) was added drop-wise over 10 min to a stirred suspension of NaH (0.034 g, 1.4 mmol) in dry THF (10 mL) under N_2. The reaction mixture was stirred until the mixture became clear (30 min; during which time, H_2 was evolved), and a solution of benzyl bromide (0.19 mL, 1.7 mmol) in THF (5 mL) was added drop-wise during 10 min. The resulting solution was refluxed for 4 h, allowed to cool and then filtered. Water (10 mL) was added and the solvents were evaporated *in vacuo*. The crude product was chromatographed [PLC on silica gel; elution with hexane-EtOAc (7:3)] to afford *diethyl 1-(N-furfurylcarbamoyl)-2-phenylethyl-phosphonate* **6a** as an orange oil (0.26 g, 56%); ν_{max}/cm^{-1}: 1675 (C=O); δ_H/ppm (300 MHz; $CDCl_3$) 1.30 (6H, t, J = 6.0 Hz, 2 × CH_3), 3.03 (1H, m, CHP), 3.08 and 3.32 (2H, 2 × m, CH_2Ph), 4.09 (4H, m, 2 × OCH_2CH_3), 4.38 (2H, m, CH_2N), 6.16 (lH, s, Ar-H), 6.28 (1H, s, Ar-H), 6.67 (lH, br s, NH) and 7.20–7.32 (6H, overlapping m, Ar-H); δ_C/ppm (75 MHz; $CDCl_3$) 16.4 (d, $J_{P\text{-}C}$ = 3.5 Hz, 2 × CH_3), 32.8 (d, J = 9.1 Hz, CH_2Ph), 36.9 (CH_2N), 48.6 (d, $J_{P\text{-}C}$ = 129.5 Hz, CHP), 62.9 (d, $J_{P\text{-}C}$ = 5.4 Hz, O$C_a$$H_2$$CH_3$), 63.2 (d, $J_{P\text{-}C}$ = 6.8 Hz, O$C_b$$H_2$$CH_3$), 107.5, 110.5, 126.7, 128.6, 128.9, 139.1, 142.1 and 151.3 (Ar-C) and 166.8 (C=O); HRMS (ESI) calc'd for $C_{18}H_{25}NO_5P$ $[M+H]^+$: 366.1470. Found 366.1466.

3.2. The general procedure for the synthesis of the N-benzylated 2-tetrahydrofuranyl derivatives *7b-e*

A solution of diethyl [*N*-(3-bromophenyl)carbamoyl]methylphosphonate **5b** (0.10 g, 0.29 mmol) in dry THF (10 mL) was added drop-wise over 10 min to a stirred suspension of NaH (0.007 g, 0.3 mmol) in dry THF (10 mL) under N_2, The reaction mixture was stirred until a clear solution was obtained (30 min; during which time H_2 was evolved). A solution of benzyl bromide (0.042 mL, 0.35 mmol) in dry THF (10 mL) was then added drop-wise during 10 min, followed by further benzyl bromide (0.19 mL, 1.7 mmol) in THF (5 mL), and the resulting solution was refluxed for 4 h. After cooling, the mixture was filtered and water (10 mL) was added to the filtrate. The solvents were evaporated *in vacuo* and the residue was chromatographed [PLC on silica gel; elution with hexane-EtOAc (1:2)] to afford *N-benzyl-N-(3-bromophenyl)-2-(tetrahydrofuran-2-yl)acetamide* **7b** as an orange oil (0.034 g, 32%); ν_{max}/cm^{-1}: 1671 (C=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.44 (2H, m, 3′-CH_2), 1.84 (2H, m, 4′-CH_2), 2.15 (1H, m, 2-CH_a), 2.45 (1H, m, 2-CH_b), 3.73 (2H, m, 5′-CH_2), 4.32 (1H, m, 2′ –CH), 4.88 (2H, m, CH_2Ph), 6.91 (lH, d,

J = 7.8 Hz, Ar-H), 7.15–7.22 (7H, overlapping m, Ar-H) and 7.43 (1H, d, J = 8.0 Hz, Ar-H); δ_C/ppm (100 MHz; $CDCl_3$) 25.8 (C-3′), 31.6 (C-4′), 40.5 (C-2), 53.1 (CH_2Ph), 67.9 (C-5′), 76.2 (C-2′), 122.8, 127.6, 127.7, 128.6, 128.7, 128.9, 129.2, 130.8, 131.3, 132.0, 137.1 and 143.7 (Ar-C) and 170.5 (C=O); HRMS (ESI) calc'd for $C_{19}H_{21}BrNO_2$ $[M+H]^+$: 374.0756. Found 374.0749.

3.3. The general procedure for the synthesis of the N-aryl-2-chloro-3-phenylpropanamides **(17)**

A mixture of 2-chloro-3-phenylpropanoic acid **14** (0.1 g, 0.5 mmol), thionyl chloride (0.08 mL, 1.08 mmol) and a catalytic amount of DMF (3 drops) was heated at 70 °C for 1 h. The resulting 2-chloro-3-phenylpropanoic acid chloride was added dropwise to a stirred cold solution of 3-bromoaniline (0.06 mL, 0.54 mmol) in DMF (1 mL), and the resulting mixture was stirred at rt overnight. Excess water was added and the mixture extracted with EtOAc (3 × 15 mL). The organic layer was dried over anhydr. $MgSO_4$, filtered and concentrated *in vacuo* to afford *N-(3-bromophenyl)-2-chloro-3-phenylpropanamide* **17b** (0.12 g, 65%) as a brown oil; ν_{max}/cm^{-1}: 1668 (C=O); δ_H/ppm (600 MHz; $CDCl_3$) 3.30 (1H, m, CH_aPh), 3.51 (1H, m, CH_bPh), 4.68 (1H, m, CHCl), 7.21–7.36 (8H, overlapping m, Ar-H), 7.73 (1H, s, Ar-H) and 8.05 (1H, s, NH); δ_C/ppm (150 MHz; $CDCl_3$) 41.5 (CH_2Ph), 61.9 (CHCl), 118.8, 122.8, 123.3, 127.6, 128.3, 128.7, 129.9, 130.5, 135.8 and 138.0 (Ar-C) and 166.4 (C=O); HRMS (ESI) calc'd for $C_{15}H_{14}BrClNO$ $[M+H]^+$: 337.9947. Found 337.9933.

3.3.1. 2-Chloro-N-(3-nitrophenyl)-3-phenylpropanamide **17f**

as a pale-yellow oil (0.31 g, 65%) following chromatography [PLC on silica gel; elution with EtOAc-hexane (5:5)]; ν_{max}/cm^{-1} 3486 (NH) and 1675 (C=O); δ_H/ppm (300 MHz; $CDCl_3$) 3.27 (1H, dd, J = 13.5 and 7.5 Hz, CH_aPh), 3.46 (1H, dd, J = 13.5 and 7.5 Hz, CH_bPh), 4.66 (1H, dd, J = 7.5 and 4.5 Hz, CHCl), 7.19–7.23 (5H, overlapping m, Ar-H), 7.45 (1H, m, Ar-H), 7.78 (1H, d, J = 9.0 Hz, Ar-H), 7.94 (1H, d, J = 7.3 Hz, Ar-H), 8.15 (1H, br s, NH) and 8.27 (1H, m, Ar-H); δ_C/ppm (75 MHz; $CDCl_3$) 41.4 (CH_2Ph), 61.7 (CHCl), 115.3, 120.0, 120.1, 127.7, 128.7, 128.9, 129.6, 130.1, 135.6 and 138.0 (Ar-C) and 166.8 (C=O); HRMS (ESI-) calc'd for $C_{15}H_{12}ClN_2O_3$ $[M-H]^-$: 303.0536. Found 303.0534.

3.4. tert-Butyldimethylsilyl ether-protected 3-aminobenzyl alcohol **18**

Imidiazole (0.48 g, 7.14 mmol) was added to a solution of 3-aminobenzyl alcohol **5b** (0.59 g, 4.8 mmol) in dry DCM at 0 °C. After stirring for 15 min, TBDMSCl (0.79 g, 5.23 mmol) was added in portions and the reaction mixture was stirred overnight at room temperature. The solution was diluted with DCM, washed with water and brine, dried over anhydr. $MgSO_4$ and evaporated *in vacuo* to afford the tert-*butyldimethylsilyl ether-protected 3-aminobenzyl alcohol* **18** (1.08 g, 95%); ν_{max}/cm^{-1}: 3340 (NH); δ_H/ppm (300 MHz; $CDCl_3$) 0.11 [6H, s, $Si(CH_3)_2$], 0.95 [9H, s, $C(CH_3)_3$], 4.67 (2H, s, CH_2OSi), 6.53 (1H, d, J = 8.7 Hz, Ar-H), 6.69–6.72 (2H, overlapping m, Ar-H) and 7.11 (1H, t, J = 8.7 Hz, Ar-H); δ_C/ppm (75 MHz; $CDCl_3$) −5.10 [$Si(CH_3)_2$], 18.6 [$C(CH_3)_3$], 26.2 [$C(CH_3)_3$], 65.1 (CH_2Ph), 112.9, 113.8, 116.4, 129.3, 142.9 and 146.5 (Ar-C); HRMS (ESI) calc'd for $C_{13}H_{24}NOSi$ $[M+H]^+$: 238.1627. Found 238.1632.

3.5. The general procedure for the preparation of propanamides **(19)**

2-Bromo-3-phenylpropanoic acid **11** (0.19 g, 0.81 mmol) was dissolved in dry DCM and CDI (0.15 g, 0.89 mmol) was added in portions. The mixture was stirred for 1 h before the *tert*-butyldimethylsilyl ether-protected amine **18** (0.19 g, 0.81 mmol) was added and stirring was continued at room temperature for 48 h. The solution was concentrated and the residue chromatographed [PLC chromatography] on silica gel; elution with hexane-EtOAc (7:3)] to afford *N*-{[3-(*tert*-butyldimethylsilyloxy)methy]phenyl}-2-bromo-3-phenylpropanamide **19h**[16] as a yellow oil (0.16 g, 60%); ν_{max}/cm^{-1}: 1678 (C=O); δ_H/ppm (300 MHz; $CDCl_3$) 0.04 [6H, s, $Si(CH_3)_2$], 0.79 [9H, s, $C(CH_3)_3$], 3.20 (1H, dd, J = 15.0 Hz and 9.0 Hz CH_bPh), 3.48 (1H, dd, J = 15.0 Hz and 6.0 Hz CH_aPh), 4.46 (1H, m, CHBr), 4.57 (2H, s, OCH_2Ph), 7.98 (1H, d, J = 8.4 Hz, Ar-H), 7.11–7.26 (7H, overlapping m, Ar-H), 7.38 (1H, s, Ar-H) and 7.71 (1H, br s, NH); δ_C/ppm (75 MHz; $CDCl_3$) −5.12 [$Si(CH_3)_2$], 18.6 [$C(CH_3)_3$], 26.1 [$C(CH_3)_3$], 29.9 (CH_2Ph), 52.0 (CHBr), 64.8 (CH_2OSi), 117.7, 118.7, 122.8, 127.5, 128.2, 128.7, 129.1, 129.6, 137.1, 142.8 (Ar-C) and 166.1 (C=O); HRMS (ESI) calc'd for $C_{22}H_{31}BrNO_2Si$ $[M+H]^+$: 448.1307. Found 448.1301.

3.5.1. 2-Bromo-N-(3-bromophenyl)-3-phenylpropanamide **19b**

as a yellow solid (0.24 g, 69%), m.p. 116–118 °C; ν_{max}/cm^{-1}: 1670 (C=O); δ_H/ppm (600 MHz; $CDCl_3$) 3.35 (1H, m, CH_aPh), 3.60 (1H, m, CH_bPh), 4.60 (1H, m, CHBr), 7.26–7.36 (8H, overlapping m, Ar-H), 7.72 (1H, s, Ar-H) and 7.82 (1H, br s, NH); δ_C/ppm (150 MHz; $CDCl_3$) 41.7 (CH_2Ph), 51.7 (CHBr), 118.7, 123.2, 127.6, 128.2, 128.8, 129.0, 129.6, 130.5, 136.6 and 138.2 (Ar-C) and 166.3 (C=O); HRMS (ESI) calc'd for $C_{15}H_{14}Br_2NO$ $[M+H]^+$: 381.9442. Found 381.9430.

3.5.2. 2-Bromo-N-[3-(hydroxymethyl)phenyl]-3-phenylpropanamide **19c**[16]

as a yellow oil (0.16 g, 60%); ν_{max}/cm^{-1}: 1669 (C=O); δ_H/ppm (300 MHz; $CDCl_3$) 3.34 (1H, dd, J = 12.0 Hz and 6.0 Hz, CH_aPh), 3.61 (1H, dd, J = 12.0 Hz and 4.5 Hz, CH_bPh), 4.61 (1H, m, CHBr), 4.67 (2H, s, OCH_2Ph), 7.14 (1H, d, J = 7.5 Hz, Ar-H), 7.25–7.31 (7H, overlapping m, Ar-H), 7.37 (1H, d, J = 8.2 Hz, Ar-H), 7.47 (1H, s, Ar-H) and 7.96 (1H, br s, NH); δ_C/ppm (150 MHz; $CDCl_3$) 41.7 (CH_2Ph), 52.0 (CHBr), 65.1 ($PhCH_2OH$), 118.7, 119.4, 123.6, 124.1, 125.0, 127.5, 128.7, 129.0, 129.6 and 130.2 (Ar-C) and 166.4 (C=O); HRMS (ESI) calc'd for $C_{16}H_{17}BrNO_2$ $[M+H]^+$: 334.0443. Found 334.0429.

3.5.3. 2-Bromo-3-phenyl-N-(2-pyridyl)propanamide **19d**

as a yellow oil (0.21 g, 62.5%); ν_{max}/cm^{-1}: 1671 (C=O); δ_H/ppm (300 MHz; $CDCl_3$) 3.24 (1H, dd, J = 13.5 Hz and 7.5 Hz, CH_aPh), 3.56 (1H, dd, J = 13.5 Hz and 7.5 Hz, CH_bPh), 4.48 (1H, m, CHBr), 7.02 (1H, m, Ar-H), 7.17–7.24 (5H, overlapping m, Ar-H), 7.67 (1H, t, J = 8.7 Hz, Ar-H), 8.12 (1H, d, J = 4.9 Hz, Ar-H), 8.21 (1H, d, J = 8.3 Hz, Ar-H) and 8.58 (1H, br s, NH); δ_C/ppm (75 MHz; $CDCl_3$) 41.3 (CH_2Ph), 49.8 (CHBr), 127.5, 128.8, 129.1, 129.5, 129.7, 129.9, 136.8, 140.4, 143.3 and 150.4 (Ar-C) and 167.6 (C=O); HRMS (ESI) calc'd for $C_{14}H_{14}BrN_2O$ $[M+H]^+$: 305.0290. Found 305.0294.

3.5.4. 2-Bromo-N-(3-hydroxyphenyl)-3-phenylpropanamide **19e**

as a brown solid (0.18 g, 63%), m.p. 118–120 °C; ν_{max}/cm^{-1}: 1677 (C=O); δ_H/ppm (300 MHz; $CDCl_3$) 3.35 (1H, dd, J = 15.0 Hz and 7.5 Hz, CH_aPh), 3.61 (1H, dd, J = 13.5 Hz and 4.5 Hz, CH_bPh), 4.61 (1H, m, CHBr), 6.68 (2H, m, Ar-H), 7.17 (1H, t, J = 8.1 Hz, Ar-H), 7.28–7.32 (5H, overlapping m, Ar-H) and 7.45 (1H, m, Ar-H); δ_C/ppm (150 MHz; $CDCl_3$) 41.9 (CH_2Ph), 51.9 (CHBr), 107.6, 111.9, 112.7, 127.6, 128.8, 129.6, 130.1, 136.6, 138.0 and 156.9 (Ar-C) and 166.8 (C=O); HRMS (ESI) calc'd for $C_{15}H_{15}BrNO_2$ $[M+H]^+$: 320.0286. Found 320.0275.

3.6. The general procedure for Arbuzov reactions of the N-aryl-2-halogeno-3-phenyl-propanamides **17b,g** and **6b-f**

A mixture of 2-bromo-*N*-[3-(hydroxymethyl)phenyl]-3-

phenylpropanamide **19c** (0.12 g, 0.35 mmol) and triethyl phosphite (0.2 mL, 1.1 mmol) under N_2 was heated under reflux at 120–150 °C for 10 h. Preparative layer chromatography of the resulting mixture [on silica gel; elution with EtOAc-hexane (6:4)] afforded *diethyl 1-[N-(3-bromophenyl)carbamoyl]-2-phenylethylphosphonate* **6b** as a pale white solid (0.086 g, 61%), m.p 108–110 °C; ν_{max}/cm^{-1}: 1671 (C=O); δ_H/ppm (600 MHz; $CDCl_3$) 1.31 (3H, t, J = 5.1 Hz, CH_3), 1.35 (3H, t, J = 5.5 Hz, CH_3), 3.13 and 3.20 (2H, 2 × m, CH_2Ph), 3.43 (1H, m, CHP), 4.16 (4H, m, 2 × OCH_2CH_3), 7.07 (1H, m, Ar-H), 7.15 (1H, m, Ar-H), 7.21–7.26 (6H, overlapping m, Ar-H), 7.72 (1H, s, Ar-H) and 8.73 (1H, br s, NH); δ_C/ppm (150 MHz; $CDCl_3$) 16.40 and 16.44 (2xd, J_{P-C} = 7.8 Hz, 2 × CH_3), 32.5 (d, J_{P-C} = 3.6 Hz, CH_2Ph), 48.6 (d, J_{P-C} = 127.1 Hz, CHP), 63.02 (d, J_{P-C} = 6.7 Hz, $OC_aH_2CH_3$), 63.67 (d, J_{P-C} = 6.7 Hz, $OC_bH_2CH_3$), 118.3, 122.6, 122.8, 126.9, 127.3, 128.6, 128.6, 128.7, 130.2 and 139.2 (Ar-C) and 165.1 (C=O); HRMS (ESI) calc'd for $C_{19}H_{24}BrNO_4P$ $[M+H]^+$: 440.0626. Found 440.0634.

3.6.1. *Diethyl 1-{N-[3-(hydroxymethyl)phenyl]carbamoyl}-2-phenylethylphosphonate* **6c**

as a yellow oil (0.068 g, 48.9%) ν_{max}/cm^{-1}: 1694 (C=O); δ_H/ppm (600 MHz; $CDCl_3$) 1.32 (6H, t, J = 6.8 Hz, 2 × CH_3), 3.28 and 3.34 (2H, 2 × m, CH_2Ph), 3.62 (1H, m, CHP), 4.10 (4H, m, 2 × OCH_2CH_3), 5.04 (2H, s, CH_2OH), 7.26–7.37 (7H, overlapping m, Ar-H), 7.50 (2H, m, Ar-H) and 8.14 (1H, br s, NH); HRMS (ESI) calc'd for $C_{20}H_{25}NO_5P$ $[M - 1]^+$: 391.1470. Found 390.1454.[17]

3.6.2. *Diethyl 1-[N-(3-hydroxyphenyl)carbamoyl]-2-phenylethylphosphonate* **6e**

as a white solid (0.095 g, 59%), m.p 158–160 °C; ν_{max}/cm^{-1}: 1677 (C=O); δ_H/ppm (600 MHz; $CDCl_3$) 1.28 and 1.29 (6H, 2xm, 2 × CH_3), 3.13 (1H, m, CHP), 3.30 and 3.36 (2H, 2 × m, CH_2Ph), 4.13 (4H, m, 2 × OCH_2CH_3), 6.56 (1H, d, J = 7.6 Hz, Ar-H), 6.84 (1H, d, J = 7.3 Hz, Ar-H) 7.16–7.26 (5H, overlapping m, Ar-H), 7.47 (1H, s, Ar-H) and 8.47 (1H, br s, NH); δ_C/ppm (150 MHz; $CDCl_3$) 16.5 (d, J_{P-C} = 5.4 Hz, 2 × CH_3), 32.8 (d, J_{P-C} = 3.2 Hz, CH_2Ph), 49.5 (d, J_{P-C} = 128.3 Hz, CHP), 63.3 (d, J_{P-C} = 6.5 Hz, $OC_aH_2CH_3$), 63.7 (d, J_{P-C} = 6.5 Hz, $OC_bH_2CH_3$), 105.9, 107.2, 111.3, 112.1, 126.9, 128.7, 128.8, 123.0, 138.7 and 157.2 (Ar-C) and 165.6 (C=O); HRMS (ESI) calc'd for $C_{19}H_{25}NO_5P$ $[M+H]^+$: 378.1470. Found 378.1468.

3.6.3. *Diethyl 1-[N-(3-nitrophenyl)carbamoyl]-2-phenylethylphosphonate* **6f**

as a yellow oil (0.050 g, 45%); ν_{max}/cm^{-1}: 1667 (C=O); δ_{HdH}/ppm (300 MHz; $CDCl_3$) 1.31 (6H, m, 2 × CH_3), 3.24 and 3.26 (2H, 2 × m, CH_2Ph), 3.48 (1H, m, CHP), 4.19 (4H, m, 2 × OCH_2CH_3), 7.13 (1H, s, Ar-H), 7.26–7.38 (5H, overlapping m, Ar-H), 7.51 (3H, m, Ar-H) and 8.6 (1H, br s, NH); δ_C/ppm (150 MHz; $CDCl_3$) 16.19 and 16.23 (2xd, J_{P-C} = 6.7 Hz, 2 × CH_3), 29.9 (CH_2Ph), 61.2 (d, J_{P-C} = 109.8 Hz, CHP), 64.7 (d, J_{P-C} = 6.0 Hz, $OC_aH_2CH_3$), 64.9 (d, J_{P-C} = 5.5 Hz, $OC_bH_2CH_3$), 115.0, 119.5, 125.8, 127.3, 127.4, 128.5, 128.6, 129.7, 129.8, 130.0, 135.4 and 138.7 (Ar-C) and 167.8 (C=O). HRMS (ESI) calc'd for $C_{19}H_{22}N_2O_7P$ $[M+OH-2H]^-$: 421.1165. Found 421.1159.

3.6.4. *Diethyl 1-(N-phenylcarbamoyl)-2-phenylethylphosphonate* **6g**

as a yellow oil (0.08 g, 25%); ν_{max}/cm^{-1}: 1678 (C=O); δ_H/ppm (300 MHz; $CDCl_3$) 1.33 (6H, m, 2 × CH_3), 3.17 and 3.22 (2H, 2 × m, CH_2Ph), 3.42 (1H, m, CHP), 4.12 (4H, m, 2 × OCH_2CH_3), 7.07 (1H, s, Ar-H), 7.20–7.32 (6H, overlapping m, Ar-H), 7.45 (2H, m, Ar-H) and 8.51 (1H, br s, NH); δ_C/ppm (150 MHz; $CDCl_3$) 16.38 and 16.42 (2 × CH_3), 32.5 (d, J_{P-C} = 4.1 Hz, CH_2Ph), 48.6 (d, J_{P-C} = 127.6 Hz CHP), 62.9 (d, J_{P-C} = 6.4 Hz, $OC_aH_2CH_3$), 63.3 (d, J_{P-C} = 6.4 Hz, $OC_bH_2CH_3$), 119.7, 120.0, 124.3, 126.7, 127.9, 128.6, 128.6, 128.8, 137.8 and 139.0 (Ar-C) and 165.0 (C=O); HRMS (ESI) calc'd for $C_{19}H_{25}NO_4P$ $[M+H]^+$: 362.1521. Found 362.1519.

3.7. *1-{N-[3-Hydroxyphenyl)carbamoyl]}-2-phenylethylphosphonic acid* **20e**

Bromotrimethylsilane (0.15 mL, 1.1 mmol) was added to a solution of diethyl 1-{*N*-[(3-bromophenyl)carbamoyl]}-2-phenylethylphosphonate **6b** (0.10 g, 0.23 mmol) in dry DCM (5 mL) at 0 °C under N_2. After 1 h, the solution was allowed to warm to room temperature and stirred for an additional 24 h. The solvent was removed *in vacuo* and the residue dissolved in THF (0.5 mL) and H_2O (0.05 mL). After stirring for 1 h, the resulting mixture was concentrated *in vacuo* and EtOAc was added to the residue; sonication of the mixture, followed by cooling at −10 °C and the formation of a dense oil. The EtOAc was decanted and the residual solvent was evaporated *in vacuo* to afford *1-{N-[3-hydroxyphenyl) carbamoyl]}-2-phenylethylphosphonic acid* **20e** as a yellow oil (0.09 g, 86%); ν_{max}/cm^{-1}: 1674 (C=O) and 3450 (OH); δ_H/ppm (600 MHz; CD_3OD) 2.99 and 3.02 (2H, 2 × m, CH_2Ph), 3.24 (1H, m, CHP), 6.38 (1H, s, Ar-H), 6.70 (1H, s, Ar-H), 6.93 (2H, m, Ar-H) and 7.06 (5H, overlapping m, Ar-H); δ_C/ppm (150 MHz; CD_3OD) 16.9 (d, J_{P-C} = 5.6 Hz, CH_2Ph), 34.1 (d, J_{P-C} = 28.6 Hz, CHP), 108.4, 108.5, 112.4, 127.6, 127.7, 129.5, 129.6, 129.7, 130.3 and 130.4 (Ar-C) and 158.8 (C=O); HRMS (ESI) calc'd for $C_{15}H_{17}NO_5P$ $[M+H]^+$: 322.0844. Found 322.0836.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.01.045.

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8. Comparative NMR spectroscopic data for the C- and non-benzylated systems (**6a** and **5a**, respectively), DEPT-135 and 2-D NMR spectra supporting the structural assignment of the fully characterised representative compound **7b**, a tentative mechanistic proposal for the formation of the unexpected series of tetrafuranyl products **7b**–**e**, and spectroscopic data for compounds **7c-e** and **8e** are provided in the Supporting Information (File I). Subsequent attempts to reproduce the formation of **8e** have, thus far, proved unsuccessful.
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15. Bioassay procedures and data are provided in the Supporting Information: File III.
16. Compound **19h** proved to be unstable, decomposing to afford compound **19c** which was purified and fully characterised.
17. The phosphonated products appear to be relatively unstable – evidenced, in this case, by an unsatisfactory ^{13}C NMR spectrum and an HRMS correlation based on a low-intensity MS peak.