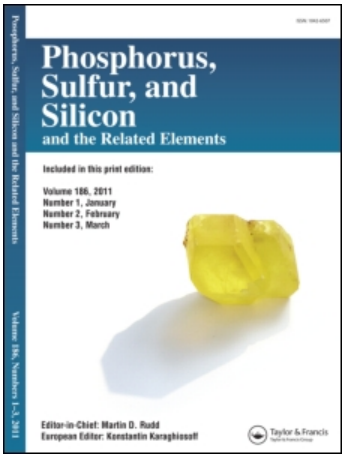
This article was downloaded by:
On: *28 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE SYNTHESIS AND FAB MASS ANALYSIS OF *O,O*-DIALKYL 1-BENZYLAMINOBENZYLPHOSPHONATES, PRECURSORS OF IMPORTANT STRUCTURAL UNITS IN ANTI-THROMBOTIC TRIPEPTIDES

Donovan Green[a]; Said Elgendy[a]; Geeta Patel[a]; Emmanuel Skordalakes[a]; Wahid Husman[a]; Vijay V. Kakkar[a]; John Deadman[a]
[a] Thrombosis Research Institute, Chelsea, London, U.K.

To cite this Article Green, Donovan , Elgendy, Said , Patel, Geeta , Skordalakes, Emmanuel , Husman, Wahid , Kakkar, Vijay V. and Deadman, John(1996) 'THE SYNTHESIS AND FAB MASS ANALYSIS OF *O,O*-DIALKYL 1-BENZYLAMINOBENZYLPHOSPHONATES, PRECURSORS OF IMPORTANT STRUCTURAL UNITS IN ANTI-THROMBOTIC TRIPEPTIDES', Phosphorus, Sulfur, and Silicon and the Related Elements, 118: 1, 271 — 291
To link to this Article: DOI: 10.1080/10426509608038819
URL: http://dx.doi.org/10.1080/10426509608038819

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 1996, Vol. 118, pp. 271–291
Reprints available directly from the publisher
Photocopying permitted by license only

© 1996 OPA (Overseas Publishers Association)
Amsterdam B.V. Published in The Netherlands
under license by Gordon and Breach Science Publishers
Printed in Malaysia

THE SYNTHESIS AND FAB MASS ANALYSIS OF *O,O*-DIALKYL 1-BENZYLAMINOBENZYLPHOSPHONATES, PRECURSORS OF IMPORTANT STRUCTURAL UNITS IN ANTI-THROMBOTIC TRIPEPTIDES

DONOVAN GREEN*, SAID ELGENDY, GEETA PATEL, EMMANUEL SKORDALAKES, WAHID HUSMAN, VIJAY V. KAKKAR and JOHN DEADMAN

Thrombosis Research Institute, Emmanuel Kaye Building, Manresa Road, Chelsea, London SW3 6LR, U.K.

(Received 23 July 1996)

Downloaded At: 18:36 28 January 2011

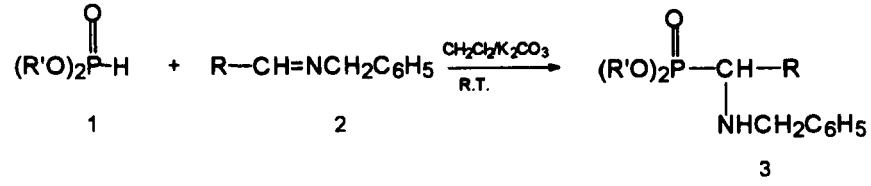
O,O-Dialkyl 1-benzylaminobenzylphosphonates (**3**) formed in quantitative yield at R.T. by the nucleophilic addition of dialkyl phosphite (**1**) to benzylidenebenzylamines (**2**) in CH_2Cl_2, give highly characteristic fragmentation patterns in their positive ion FAB mass spectrum. Catalytic hydrogenolysis of these precursors produces 'P1' structural units which when incorporated into substrate-like peptides, form potent inhibitors of thrombin.

Keywords: *O*;*O*-Dialkyl 1-Benzylaminobenzylphosphonates; FAB mass spectrum; thrombin inhibition

INTRODUCTION

O,O-Dialkyl 1-benzylaminobenzylphosphonates (**3**) have gained important significance as precursors of analogues of aminocarboxylic acids and their esters;[1] and also as structural units in synthetic or naturally occurring phosphonopeptides.[2] The compounds are isolated as bright yellow, highly viscous oils or crystalline solids.

*Corresponding author.



The benzylidenebenzylamine precursors (**2**) were easily prepared by the addition of a solution of the aromatic aldehyde (1 mol equivalent) in CH_2Cl_2 to a solution of benzylamine also in CH_2Cl_2 (1 mol equivalent), in the presence of excess anhydrous K_2CO_3 (a similar approach has been used to prepare benzylidene-diphenylmethylamines which are useful substrates for conversion to 1-aminobenzylphosphonic acids).[3] After filtering off the desiccant and removing excess solvent (under reduced pressure), the compounds (**2**) were isolated in quantitative yield as brightly colored crystalline solids; before being smoothly converted to their benzylaminophosphonate analogues (**3**).

Downloaded At: 18:36 28 January 2011

RESULTS AND DISCUSSION

The ^1H N.M.R. spectra of the benzylidenebenzylamines are marked by a low field singlet resonating at approximately 9.00 ppm for the imino proton CH = N, which becomes the α-CH doublet in the phosphonate; and a higher field singlet at approximately 5.00 ppm for the aminomethylene peak $NHCH_2$, which becomes a symmetrical AB doublet (characteristic of gem proton coupling), in the product. As a result of their stability, the compounds (**2**) are extremely good substrates for conversion to the corresponding benzylaminophosphonates (**3**).

The *O,O*-dialkyl 1-benzyaminobenzylphosphonates were generally prepared at ambient temperature by the nucleophilic addition of dialkyl phosphite to a solution of the benzylidenebenzylamine in CH_2Cl_2. Only in the case of the pentafluorobenzylphosphonate derivatives (entries 30, 31, 32 in the table) was it found necessary to heat the reaction mixture (to 50°C), to facilitate formation of the phosphonate. No attempt was made to catalyze the reaction;[4] the products being isolated in quantitative yield.

As in the case of the dialkyl α-hydroxybenzyl- and dialkyl α-methoxybenzylphosphonates,[5,6] the dialkoxy groups of the benzylaminobenzylphosphonates exhibit magnetic non-equivalence in their ^1H and ^{13}C N.M.R. spectra. These signals resonate as distinct pairs in the spectra and probably arise as a result of the dominant effect of the phosphorus bonded chiral α carbon atom.

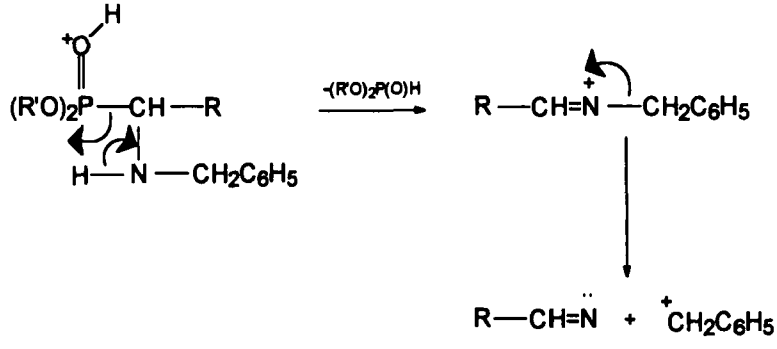
Fast atom bombardment mass spectrometry (FABMS) of these phosphonates gave rise to the characteristic $[M + H]^+$ fragment, and provided a valuable confirmatory aid in the authentication of their structure (see Table). A major

TABLE Principal ions in the FAB mass spectra of *O,O*-dialkyl 1-benzylaminobenzylphosphonates (**3**)

Entry	*R*	*R'*	*$[M + H]^+$ m/z(%)*	*$[M + H\text{-}(RO)_2P(O)H]^+$ m/z(%)*	*$\delta\ ^{31}P$/ppm ($CDCl_3$)*
1	C_6H_5	CH_3	306 (17)	196(100)	26.50
2	C_6H_5	CH_3CH_2	334(14)	196 (100)	24.25
3	C_6H_5	$CH_3(CH_2)_2$	362 (36)	196 (100)	24.01
4	4-$NO_2C_6H_4$	CH_3	351 (13)	241 (45)	24.79
5	4-$NO_2C_6H_4$	C_6H_5	474 (32)	241 (100)	15.26
6	4-$CH_3OC_6H_4$	CH_3	336 (15)	226 (100)	26.84
7	4-$CH_3OC_6H_4$	CH_3CH_2	364 (21)	226 (100)	24.52
8	4-$CH_3OC_6H_4$	$(CH_3)_2CH$	392 (45)	226 (100)	22.89
9	2-HOC_6H_4	CH_3	320 (32)	210 (14)	25.01
10	2-HOC_6H_4	CH_3CH_2	348 (10)	210 (27)	22.66
11	2-HOC_6H_4	C_6H_5	441 (1)	210 (4)	26.34
12	2-HOC_6H_4	$C_6H_5CH_2$	472 (27)	210 (21)	23.61
13	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	396 (18)	286 (100)	26.36
14	3,4,5-$(CH_3O)_3C_6H_2$	CH_3CH_2	424 (15)	286 (100)	24.09
15	3,4,5-$(CH_3O)_3C_6H_2$	C_6H_5	520 (5)	286 (100)	16.92
16	4-FC_6H_4	CH_3	324 (22)	214 (96)	26.20
17	4-FC_6H_4	CH_3CH_2	352 (33)	214 (100)	23.93
18	4-FC_6H_4	$C_6H_5CH_2$	476 (14)	214 (100)	24.82
19	4-$CF_3C_6H_4$	CH_3	374 (32)	264 (100)	25.44
20	4-$CF_3C_6H_4$	CH_3CH_2	402 (11)	264 (100)	23.14
21	4-$CF_3C_6H_4$	$C_6H_5CH_2$	526 (26)	264 (100)	24.14
22	4-$(CH_3)_2NC_6H_4$	CH_3	349 (5)	239 (100)	27.15
23	4-$(CH_3)_2NC_6H_4$	CH_3CH_2	399 (32)	239 (100)	24.93
24	4-$(CH_3)_2NC_6H_4$	$C_6H_5CH_2$	501 (2)	239 (100)	25.92
25	4-ClC_6H_4	CH_3	340 (27)	230 (100)	25.99
26	4-ClC_6H_4	CH_3CH_2	368 (31)	230 (7)	23.58
27	4-ClC_6H_4	$(CH_3)_2CH$	396 (9)	230 (100)	21.87
28	4-ClC_6H_4	C_6H_5	464 (23)	230 (100)	16.50
29	4-ClC_6H_4	$C_6H_5CH_2$	492 (12)	230 (100)	24.50
30	C_6F_5	CH_3CH_2	424 (18)	286 (100)	20.01
31	C_6F_5	$(CH_3)_2CH$	452 (33)	286 (100)	18.31
32	C_6F_5	$CH_3\ (CH_2)_3$	480 (38)	286 (100)	20.24
33	4-BrC_6H_4	$(CH_3)_2CH$	441 (21)	275 (77)	21.68
34	4-BrC_6H_4	C_6H_5	509 (7)	275 (67)	16.38
35	4-$CH_3CO_2C_6H_4$	CH_3CH_2	392 (12)	254 (100)	23.19
36	4-$CH_3CO_2C_6H_4$	C_6H_5	488 (7)	254 (100)	16.02
37	3-$CF_3OC_6H_4$	CH_3CH_2	418 (25)	280 (100)	23.18
38	4-NC_5H_5	CH_3	307 (42)	197 (55)	24.78
39	4-NC_5H_5	CH_3CH_2	335 (63)	197 (100)	22.40
40	4-NC_5H_5	$C_6H_5CH_2$	459 (12)	197 (42)	12.37

Downloaded At: 18:36 28 January 2011

fragment observed was the elimination of dialkyl phosphite from the $[M + H]^+$ ion by a process of P-Cα cleavage and proton transfer (see Scheme).[7] This fragment was often the base peak. Despite the range of dialkoxy groups used to protect phosphorus (as shown in the table), there was no evidence in the FAB mass spectra for sequential loss of one alkoxy group over another; suggesting that the ready loss of neutral dialkyl phosphite is a favourable event. An additional fragment was generated by further N-C fission, with the loss of $C_6H_5CH_2^+$ (m/z 91), and rearrangement of this species to the more stable tropylium ion.



A number of biologically active *O,O*-dialkyl 1-hydroxyiminoalkanephosphonates[8] have also been prepared in this laboratory as precursors of important 'P1' structural units in dialkyldipeptidylaminophosphonate anti-thrombotic agents.[9] These gave the $[M + H]^+$ ion as the base peak in the FAB mass spectrum, but interestingly no other fragments arising from P-Cα cleavage or proton transfer were observed (results to be published). In this comparison, the observation of definitive fragmentation patterns in the FAB mass spectra of benzylaminophosphonates is a useful diagnostic aid, and allows for differentiation between other α-functionalised phosphonates.

In light of our observations a variety of benzylaminobenzylphosphonates have been subjected to catalytic hydrogenolysis over 10% Pd/C, and used to form a number of anti-thrombotic phosphonotripeptides that exploit the hydrophobic 'P1' interaction that occurs between 'fibrinogen-like' peptide analogues and thrombin's specificity pocket.[10] The benzylaminobenzylphosphonates are therefore an attractive 'P1' precursor structure, in view of the therapeutic efficacy which is desired. Where qualitative information concerned with phosphorus derived 'P1' structural units or their derivatives is available (as in the case of FABMS), this is very useful. Earlier attempts to authenticate the structure of these benzylaminophosphonates by: electron impact or chemical ionisation mass

Downloaded At: 18:36 28 January 2011

spectrometry gave little or no information at all. However application of FAB mass spectrometry gave clear, highly characteristic fragmentation patterns that enabled us to quickly choose suitable candidates for subjection to reduction. As indicated by the wide range of compounds that were analysed, one observed that these fragmentations were consistent for this class of compound; irrespective of the substituent carried by the aromatic ring, or variation of the dialkoxy groups on phosphorus.

EXPERIMENTAL

^{1}H, ^{13}C, ^{31}P and where appropriate ^{19}F N.M.R. spectra, were recorded on a Bruker AMX 400 spectrometer. C,H,N determinations were carried out on a Carlo Erba Model 1106 Elemental Analyser. Low resolution FAB mass spectra were obtained in a matrix of 3-nitrobenzyl alcohol on a VG ZAB SE reverse geometry mass spectrometer operating at a resolution of a 1000 units. A primary beam of xenon atoms was produced from an ion gun operating at 8 kV. Exact mass FAB mass spectra were obtained using the above spectrometer and ionisation conditions described earlier, at a resolution of 10 000 units. The exact masses were measured by the technique known as peak matching, using glycerol as the reference.

Downloaded At: 18:36 28 January 2011

Preparation of O,O-Dialkyl 1-benzylaminobenzylphosphonates

The phosphonates were prepared by adding dialkyl phosphite (1 mol equivalent) to the corresponding benzylidenebenzylamine (1 mol equivalent) and allowing the mixture to stir overnight at room temperature. The products were obtained as brightly colored, extremely viscous oils or solids, in quantitative yield. Compounds 30, 31 and 32 were obtained by heating the phosphites with the corresponding benzylidenebenzylamine at 50°C under an argon atmosphere for 2 hours. The final products were isolated in quantitative yield as very thick viscous oils.

O,O-Dimethyl 1-benzylaminobenzylphosphonate (1)

(**3**, R′ = CH_3, R = C_6H_5) C,H,N (Found: C, 62.64; H, 6.85; N, 4.51. Calc. for $C_{16}H_{20}NO_3P$: C, 62.95; H, 6.56; N, 4.59%); ^{1}H ($CDCl_3$) δ 2.41 (s, br, 1H, $NHCH_2$), 3.53 (d, 3H, CH_3O, $^{3}J_{POCH}$ 10.43), 3.73 (d, 3H, CH_3O, $^{3}J_{POCH}$ 10.53), 3.53 (d, 1H, $NHCH_2$ gem $^{2}J_{HCH}$ 13.90), 3.80 (d, 1H, $NHCH_2$ gem $^{2}J_{HCH}$ 13.27),

4.05 (d, 1H, P-CH, $^2J_{PCH}$ 20.22), 7.23–7.45 (m, 10H, C_6H_5x2); ^{13}C ($CDCl_3$) δ 51.14 (d, $NHCH_2$, $^3J_{PCNC}$ 17.55), 53.43 (d, CH_3O, $^2J_{POC}$ 6.98), 53.74 (d, CH_3O, $^2J_{POC}$ 7.04), 59.27 (d, P-CH, $^1J_{PC}$ 154.10), 127.19–128.97 (aromatic envelope), 135.46 (d, P-CH-Cq, $^2J_{PCC}$ 3.65), 139.16 (s, CH_2-Cq of benzylamino ring); $^{31}P(CDCl_3)$: δ 26.50; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 306.1255. $C_{16}H_{21}NO_3P$ requires 306.1259. $[M + H - (CH_3O)_2P(O)H]^+$ 196.1122. $C_{14}H_{14}N$ requires 196.1126.

O,O-Diethyl 1-benzylaminobenzylphosphonate (2)

(**3**, R′ = CH_3CH_2, R = C_6H_5) C,H,N (Found: C, 64.76; H, 7.44; N, 4.32. Calc. for $C_{18}H_{24}NO_3P$: C, 64.87; H, 7.21; N, 4.20%); $^1H(CDCl_3)$ δ 1.11 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 6.72), 1.26 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.08), 2.53 (s, br, 1H, $NHCH_2$), 3.53 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.30), 3.80 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.31), 3.84–4.18 (m, 5H, CH_3CH_2Ox2 overlapping P-CH), 7.19–7.45 (m, 10H, C_6H_5x2); $^{13}C(CDCl_3)$: δ 16.22 (d, CH_3CH_2O, $^3J_{POCC}$ 5.35), 16.41 (d, CH_3CH_2O, $^3J_{POCC}$ 6.04), 51.18 (d, $NHCH_2$, $^3J_{PCNC}$ 17.42), 59.58 (d, P-CH, $^1J_{PC}$ 153.53), 62.74 (d, CH_3CH_2O, $^2J_{POC}$ 6.86), 62.92 (d, CH_3CH_2O, $^2J_{POC}$ 6.98), 126.94–128.72 (aromatic envelope), 135.74 (d, P-CH-Cq, $^2J_{PCC}$ 3.96), 139.32 (s, CH_2-Cq of benzylamino ring); $^{31}P(CDCl_3)$ δ 24.25; FAB acc.ms (3-NOBA): m/z(%) Found: $[M + H]^+$ 334.1576. $C_{18}H_{25}NO_3P$ requires 334.1572. $[M + H - (CH_3CH_2O)_2P(O)H]^+$ 196.1123. $C_{14}H_{14}N$ requires 196.1126.

O,O-Di-n-propyl 1-benzylaminobenzylphosphonate (3)

(**3**, R′ = $CH_3(CH_2)_2$, R = C_6H_5) C,H,N (Found: C, 66.58; H, 7.98; N, 3.42. Calc. for $C_{20}H_{28}NO_3P$: C, 66.48; H, 7.76; N, 3.88%); $^1H(CDCl_3)$ δ 0.70 (t, 3H, $CH_3(CH_2)_2O$, $^3J_{HCCH}$ 7.40), 0.91 (t, 3H, $CH_3(CH_2)_2O$, $^3J_{HCCH}$ 7.39), 1.49 (m, 2H, CH_2CH_2O, $^3J_{HCCH}$ 7.18), 1.64 (m, 2H, CH_2CH_2O, $^3J_{HCCH}$ 7.20), 2.78 (s, br, 1H, $NHCH_2$), 3.52–4.07 (m, 7H, P-CH, $NHCH_2$, $CH_3CH_2CH_2Ox2$ all overlapping), 7.20–7.45 (m, 10H, C_6H_5x2); $^{13}C(CDCl_3)$: δ 9.88 (s, $CH_3(CH_2)_2O$), 10.01 (s, $CH_3(CH_2)_2O$), 23.75 (d, $CH_3CH_2CH_2O$, $^3J_{POCC}$ 5.98), 23.91 (d, $CH_3CH_2CH_2O$, $^3J_{POCC}$ 5.91), 51.13 (d, $NHCH_2$, $^3J_{PCNC}$ 17.23), 59.45 (d, P-CH, $^1J_{PC}$ 153.97), 68.19 (d, CH_2O, $^2J_{POC}$ 7.04), 68.39 (d, CH_2O, $^2J_{POC}$ 7.23), 127.14–128.96 (aromatic envelope), 135.72 (d, P-CHCq, $^2J_{PCC}$ 3.77), 139.20 (s, CH_2Cq of benzylamino ring); $^{31}P(CDCl_3)$: δ 24.01; FAB acc.ms (3-NOBA): m/z(%) Found: $[M + H]^+$ 362.1882. $C_{20}H_{29}NO_3P$ requires 362.1885. $[M + H - (CH_3(CH_2)_2O)_2P(O)H]^+$ 196.1122. $C_{14}H_{14}N$ requires 196.1126.

Downloaded At: 18:36 28 January 2011

***O,O-Dimethyl 1-benzylamino 4'-nitrobenzylphosphonate* (4)**

(**3**, R′ = CH_3, R = 4-$NO_2C_6H_4$) C,H,N (Found: C, 54.52; H, 5.43; N, 7.81. Calc. for $C_{16}H_{19}N_2O_5P$: C, 54.86; H, 5.43; N, 8.00%); ^{1}H($CDCl_3$): δ 2.40 (s, br, 1H, $NHCH_2$), 3.53 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.32), 3.80 (d, 1H, $NHCH_2$ gem $^2J_{HCH}$ 13.58), 3.65 (d, 3H, CH_3O, $^3J_{POCH}$ 10.66), 3.75 (d, 3H, CH_3O, $^3J_{POCH}$ 10.66), 4.19 (d, 1H, P-CH, $^2J_{PCH}$ 21.04), 7.21–7.36 (m, 5H, C_6H_5), 7.63 (dd, 2H, H_3,H_4 of nitrobenzyl ring, $^3J_{HCCH}$ 8.84), 8.24 (d, 2H, H_2,H_6 of nitrobenzyl ring, $^3J_{HCCH}$ 8.72); ^{13}C($CDCl_3$): δ 51.56 (d, $NHCH_2$, $^3J_{PCNC}$ 16.60), 53.63 (d, CH_3O, $^2J_{POC}$ 6.86), 53.90 (d, CH_3O, $^2J_{POC}$ 7.11), 59.12 (d, P-CH, $^1J_{PC}$ 151.64), 123.74–129.51 (aromatic envelope), 138.57 (s, CH_2Cq of benzylamino ring), 143.67 (d, P-CHCq, $^2J_{PCC}$ 4.34), 147.74 (s, C_4-NO_2); ^{31}P($CDCl_3$): δ 24.79; FAB acc.ms(3-NOBA): m/z(%). Found: $[M + H]^+$ 351.1113. $C_{16}H_{20}N_2O_5P$ requires 351.1110. $[M + H - (CH_3O)_2P(O)H]^+$ 241.0974. $C_{14}H_{13}N_2O_2$ requires 241.0977.

***O,O-Diphenyl 1-benzylamino 4'-nitrobenzylphosphonate* (5)**

(**3**, R′ = C_6H_5, R = 4-NO_2- C_6H_4) C,H,N (Found: C, 65.41; H, 4.69; N, 6.03. Calc. for $C_{26}H_{23}N_2O_5P$: C, 65.82; H, 4.85; N, 5.91%); ^{1}H($CDCl_3$): δ 2.59 (s, br, 1H, $NHCH_2$), 3.60 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.33), 3.78 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.34), 4.51 (d, 1H, P-CH $^2J_{PCH}$ 20.94), 6.93–7.36 (m, 15H, C_6H_5x3), 7.72 (dd, 2H, H_2, H_6, $^3J_{HCCH}$ 8.82), 8.24 (d, 2H, H_3, H_5, $^3J_{HCCH}$ 8.43); ^{13}C($CDCl_3$): δ 51.45 (d, $NHCH_2$, $^3J_{PCNC}$ 17.67), 59.14 (d, P-CH, $^1J_{PC}$ 154.66), 120.20–129.86 (aromatic envelope), 138.22 (s, CH_2Cq), 142.75 (d, P-CHCq, $^2J_{PCC}$ 3.90), 147.88 (d, P-OC_6H_5, Cq, $^2J_{POC}$ 3.27), 150.00 (d, P-OC_6H_5, Cq, $^2J_{POC}$ 3.81); ^{31}P($CDCl_3$): δ 15.26; FAB acc.ms(3-NOBA): m/z(%). Found: $[M + H]^+$ 475.1426. $C_{26}H_{24}N_2O_5P$ requires 475.1423. $[M + H - (C_6H_5O)_2P(O)H]^+$ 241.0974. $C_{14}H_{13}N_2O_2$ requires 241.0977.

***O,O-Dimethyl 1-benzylamino 4'-methoxybenzylphosphonate* (6)**

(**3**, R′ = CH_3, R = 4-$CH_3OC_6H_4$) C,H,N (C, 60.55; H, 6.26; N, 3.85. Calc. for $C_{17}H_{22}NO_4P$: C, 60.90; H, 6.57; N, 4.18%); ^{1}H($CDCl_3$): δ 2.27 (s, br, 1H, $NHCH_2$), 3.54 (d, 3H, CH_3O, $^3J_{POCH}$ 10.38), 3.72 (d, 3H, CH_3O, $^3J_{POCH}$ 10.50), 3.79 (s, 3H, OCH_3), 3.99 (d, 1H, P-CH, $^2J_{PCH}$ 19.62), 6.91 (d, 2H, H_2, H_6 of methoxybenzyl ring, $^3J_{HCCH}$ 8.68), 7.22–7.37 (m, 7H, H_3, H_5, overlapping C_6H_5); ^{13}C($CDCl_3$): δ 50.98 (d, $NHCH_2$, $^3J_{PCNC}$ 17.61), 53.39 (d, CH_3O, $^2J_{POC}$ 6.92), 53.65 (d, CH_3O, $^2J_{POC}$ 7.23), 55.20 (s, OCH_3), 58.50 (d, P-CH, $^1J_{PC}$

Downloaded At: 18:36 28 January 2011

155.67), 123–129.78 (aromatic envelope), 139.27 (s, CH_2-Cq), 159.44 (d, P-CHCq, $^2J_{PCC}$ 2.39), 161.24 (s, C_4-OCH_3); $^{31}P(CDCl_3)$: δ 26.85; FAB acc.ms(3-NOBA): m/z(%). Found: $[M + H]^+$ 336.1362. $C_{17}H_{23}NO_4P$ requires 336.1365. $[M + H\text{-}(CH_3O)_2P(O)H]^+$ 226.1234. $C_{15}H_{16}NO$ requires 226.1232.

O,O-Diethyl 1-benzylamino 4'-methoxybenzylphosphonate (7)

(**3**, R′ = CH_3CH_2, R = 4-$CH_3OC_6H_4$) C,H,N (C, 61.12; H, 7.08; N, 3.95. Calc. for $C_{19}H_{26}NO_4P$: C, 62.81; H, 7.16; N, 3.86%); $^1H(CDCl_3)$: δ 1.43 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.07), 1.48 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.07), 2.26 (s, br, 1H, $NHCH_2$), 3.81 (s, 3H, OCH_3), 3.96 (d, 1H, P-CH, $^2J_{PCH}$ 19.48), 3.99–4.10 (m, 4H, CH_3CH_2Ox2), 6.91 (d, 2H, H_2,H_3 of methoxybenzyl ring, $^3J_{HCCH}$ 7.49), 7.22–7.35 (m, 7H, H_3, H_5 overlapping C_6H_5); $^{13}C(CDCl_3)$: δ 16.31 (d, CH_3CH_2O, $^3J_{POCC}$ 5.77), 16.46 (d, CH_3CH_2O, $^3J_{POCC}$ 5.80), 51.03 (d, $NHCH_2$, $^3J_{PCNC}$ 17.44), 55.23 (s, CH_3O), 58.79 (d, P-CH, $^1J_{PC}$ 154.93), 62.72 (d, CH_3CH_2O, $^2J_{POC}$ 6.94), 62.87 (d, CH_3CH_2O, $^2J_{POC}$ 7.00), 123.90–129.81 (aromatic envelope), 139.38 (s, CH_2Cq), 159.32 (d, P-CHCq, $^2J_{PCC}$ 3.17), 190.80 (s, C_4-OCH_3); $^{31}P(CDCl_3)$: δ 24.52; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 364.1675 $C_{19}H_{27}NO_4P$ requires 364.1678. $[M + H - (CH_3CH_2O)_2P(O)H]^+$ 226.1235. $C_{15}H_{16}NO$ requires 226.1232.

O,O-Di-isopropyl 1-benzylamino 4'-methoxybenzylphosphonate (8)

(**3**, R′ = $(CH_3)_2CH$, R = 4-$CH_3OC_6H_4$) C,H,N (Found: C, 64.27; H, 7.31; N, 3.91. Calc. for $C_{21}H_{30}NO_4P$: C, 64.45; H, 7.67; N, 3.58%); $^1H(CDCl_3)$: δ 1.23 (dd, 6H, $(CH_3)_2CH$, $^3J_{HCCH}$ 6.19), 1.28 (dd, 6H, $(CH_3)_2CH$, $^3J_{HCCH}$ 6.18), 2.56 (s, br, 1H, $NHCH_2$), 3.81 (s, 3H, OCH_3), 3.89 (d, 1H, P-CH, $^2J_{PCH}$ 19.80), 4.45–5.52 (m, 2H, $(CH_3)_2CHOx2$), 6.90 (d, 2H, H_2, H_6 of methoxybenzylphosphonate ring, $^3J_{HCCH}$ 8.55), 7.21–7.36 (m, 7H, H_3, H_5 overlapping C_6H_5); $^{13}C(CDCl_3)$: δ 24.34 (d, $(CH_3)_2CH$, $^3J_{POCC}$ 5.52), 24.58 (d, $(CH_3)_2CH$, $^3J_{POCC}$ 5.31), 51.52 (d, $NHCH_2$, $^3J_{PCNC}$ 17.77), 55.63 (s, C_4-OCH_3), 59.70 (d, P-CH, $^1J_{PC}$ 156.78), 71.59 (d, $(CH_3)_2CH$, $^2J_{POC}$ 7.19), 71.62 (d, $(CH_3)_2CH$, $^2J_{POC}$ 7.32), 124.12–130.39 (aromatic envelope), 139.93 (s, CH_2Cq), 159.61 (d, P-CHCq, $^2J_{PCC}$ 2.91), 191.20 (s, C_4-OCH_3); $^{31}P(CDCl_3)$: δ 22.89; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 392.1994. $C_{21}H_{31}NO_4P$ requires 392.1991. $[M + H - ((CH_3)_2CHO)_2P(O)H]^+$ 226.1235. $C_{15}H_{16}NO$ requires 226.1232.

Downloaded At: 18:36 28 January 2011

***O,O-Dimethyl 1-benzylamino 2'-hydroxybenzylphosphonate* (9)**

(**3**, R′ = CH_3, R = 2-HOC_6H_4) C,H,N (Found: C, 59.69; H, 5.82; N, 3.95. Calc. for $C_{16}H_{20}NO_4P$: C, 59.81; H, 6.23; N, 4.36%); $^1H(CDCl_3)$: δ 2,73 (s, br, 1H, $NHCH_2$), 3.54 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 11.58), 3.94 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.04), 3.68 (d, 3H, CH_3O, $^3J_{POCH}$ 10.56), 3.79 (d, 3H, CH_3O, $^3J_{POCH}$ 11.86), 4.24 (d, 1H, P-CH, $^2J_{PCH}$ 19.06), 6.82–7.45 (m, 9H, aromatic envelope), 10.98 (s, br, 1H, C_2-OH); $^{13}C(CDCl_3)$: δ 51.87 (d, $NHCH_2$, $^3J_{PCNC}$ 17.11), 53.81 (d, CH_3O, $^2J_{POC}$ 6.98), 59.69 (d, P-CH, $^1J_{PC}$ 150.89), 126.12–132.37 (aromatic envelope), 137.23 (s, CH_2Cq), 158.05 (d, P-CHCq $^2J_{PCC}$ 5.03), 165.62 (s, C_2-OH); $^{31}P(CDCl_3)$ δ 25.01; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 322.1205. $C_{16}H_{21}NO_4P$ requires 322.1208. $[M + H - (CH_3O)_2P(O)H]^+$ 212.1071. $C_{14}H_{14}NO$ requires 212.1075.

***O,O-Diethyl 1-benzylamino 2'-hydroxybenzylphosphonate* (10)**

(**3**, R′ = CH_3CH_2, R = 2-HOC_6H_4) C,H,N (Found: C, 61.54; H, 6.47; N, 3.90. Calc. for $C_{18}H_{24}NO_4P$: C, 61.89; H, 6.88; N, 4.01%); $^1H(CDCl_3)$: δ 1.23 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.07), 1.24 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.09), 2.72 (s, br, 1H, $NHCH_2$), 3.60 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.13), 3.92–4.15 (m, 5H, CH_3CH_2Ox2 overlapping P-CH), 6.71–7.43 (m, 9H, aromatic envelope), 11.01 (s, br, 1H, C_2-OH); $^{13}C(CDCl_3)$: δ 16.32 (d, CH_3CH_2Ox2, $^3J_{POCC}$ 5.77), 51.92 (d, $NHCH_2$, $^3J_{PCNC}$ 16.99), 60.12 (d, P-CH, $^1J_{PC}$ 150.41), 126.34–130.49 (aromatic envelope), 137.40 (s, CH_2Cq), 158.09 (d, P-CHCq, $^2J_{PCC}$ 4.78); $^{31}P(CDCl_3)$: δ 22.66; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 350.1524. $C_{18}H_{25}NO_4P$ requires 350.1521. $[M + H - (CH_3CH_2O)_2P(O)H]^+$ 212.1072. $C_{14}H_{14}NO$ requires 212.1075.

***O,O-Diphenyl 1-benzylamino 2'-hydroxybenzylphosphonate* (11)**

(**3**, R′ = C_6H_5, R = 2-HOC_6H_4) C,H,N (Found: C, 70.46; H, 5.71; N, 3.18. Calc. for $C_{26}H_{24}NO_4P$: C, 70.11; H, 5.39; N, 3.15%); $^1H(CDCl_3)$: δ 3.61 (d, 1H, $NHCH_2$ gem $^2J_{HCH}$ 13.32), 3.80 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.41), 4.02 (d, 1H, P-CH, $^2J_{PCH}$ 19.61), 6.73–7.53 (m, 19H, aromatic envelope), 9.41 (s, br, 1H, C_2-OH); $^{13}C(CDCl_3)$: δ 51.03 (d, $NHCH_2$, $^3J_{PCNC}$ 16.94), 60.11 (d, P-CH, $^1J_{PC}$ 152.66), 115.22–129.57 (aromatic envelope), 157.34 (s, C_2-OH); $^{31}P(CDCl_3)$: δ 26.34; FAB acc.ms.(3-NOBA): m/z(%) Found: $[M + H]^+$ 446.1525. $C_{26}H_{25}NO_4P$ requires 446.1521. $[M + H - (C_6H_5O)_2P(O)H]^+$ 212.1072. $C_{14}H_{14}NO$ requires 212.1075.

Downloaded At: 18:36 28 January 2011

***O,O-Dibenzyl 1-benzylamino 2'-hydroxybenzylphosphonate* (12)**

(**3**, R′ = $C_6H_5CH_2$, R = 2-HOC_6H_4) C,H,N (Found: C, 71.43; H, 6.08; N, 2.97. Calc. for $C_{28}H_{28}NO_4P$: C, 71.04; H, 5.92, N, 2.96%); $^1H(CDCl_3)$: δ 3.52 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.25), 3.87 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.06), 4.24 (d, 1H, P-CH, $^2J_{PCH}$ 19.10), 4.80–4.92 (m, 4H, $C_6H_5CH_2Ox2$), 6.80–7.35 (m, 19H, aromatic envelope); $^{13}C(CDCl_3)$: δ 51.72 (d, $NHCH_2$, $^3J_{PCNC}$ 17.05), 59.40 (d, P-CH, $^1J_{PC}$ 151.39), 68.96 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 7.11), 69.07(d, $C_6H_5CH_2O$, $^2J_{POC}$ 7.04), 126.47–135.90 (aromatic envelope), 138.58 (s, CH_2Cq), 157.83 (d, P-CHCq, $^2J_{PCC}$), 165.87 (s, C_2-OH); $^{31}P(CDCl_3)$: δ 23.61; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 474.1837. $C_{28}H_{29}NO_4P$ requires 474.1834. $[M + H - (C_6H_5CH_2O)_2P(O)H]^+$ 212.1071. $C_{14}H_{14}NO$ requires 212.1075.

***O,O-Dimethyl 1-benzylamino 3'4'5'-trimethoxybenzylphosphonate* (13)**

(**3**, R′ = CH_3, R = 3,4,5-$(CH_3O)_3C_6H_2$) C,H,N (Found: C, 57.74; H, 6.84; N, 3.37. Calc. for $C_{19}H_{26}NO_6P$: C, 57.72; H, 6.58; N, 3.54%); $^1H(CDCl_3)$: δ 2.46 (s, br, 1H, $NHCH_2$), 3.55 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.30), 3.57 (d, 3H, CH_3O, $^3J_{POCH}$ 10.48), 3.77 (d, 3H, CH_3O, $^3J_{POCH}$ 10.58), 3.84 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.26), 3.87 (s, 9H, CH_3Ox3), 3.97 (d, 1H, P-CH $^2J_{PCH}$ 20.19), 6.66 (s, 1H, H-ortho), 6.67 (s, 1H, H-ortho), 7.25–7.36 (m, 5H, C_6H_5); $^{13}C(CDCl_3)$: δ 50.99 (d, $NHCH_2$, $^3J_{PCNC}$ 17.30), 53.27 (d, CH_3O, $^2J_{POC}$ 7.04), 53.65 (d, CH_3O, $^2J_{POC}$ 6.98), 56.03 (s, CH_3Ox3), 59.16 (d, P-CH, $^1J_{PC}$ 154.91), 103.36 (C-ortho of trimethoxybenzyl ring), 105.47 (C-ortho of trimethoxybenzyl ring), 127.08–128.26 (aromatic envelope), 130.73 (C-meta of trimethoxybenzyl ring), 130.79 (C-meta of trimethoxybenzyl ring), 137.53 (C-para of trimethoxybenzyl ring), 138.98 (s, CH_2Cq), 153.19 (d, P-CHCq, $^2J_{PCC}$ 2.39); $^{31}P(CDCl_3)$ δ 26.36; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 396.1572. $C_{19}H_{27}NO_6P$ requires 396.1576. $[M + H - (CH_3O)_2P(O)H]^+$ 286.1446. $C_{17}H_{20}NO_3$ requires 286.1443.

***O,O-Diethyl 1-benzylamino 3',4',5'-trimethoxybenzylphosphonate* (14).**

(**3**, R′ = CH_3CH_2, R = 3,4,5-$(CH_3O)_3C_6H_2$) C,H,N (Found: C, 59.26; H, 7.22; N, 3.52. Calc. for $C_{21}H_{30}NO_6P$: C, 59.58; H, 7.09; N, 3.31%); $^1H(CDCl_3)$: δ 1.18 (t, 3H, CH_3CH_2, $^3J_{HCCH}$ 7.07), 1.36 (t, 3H, CH_3CH_2, $^3J_{HCCH}$ 7.08), 2.40 (s, br, 1H, $NHCH_2$), 3.58 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.37), 3.83 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.64), 3.87 (s, 9H, CH_3Ox3), 3.98–4.21 (m, 5H, CH_3CH_2Ox2 overlapping P-CH), 6.67 (s, 1H, H-ortho), 6.68 (s, 1H, H-ortho), 7.25–7.35 (m, 5H, C_6H_5); $^{13}C(CDCl_3)$: δ 16.19 (d, CH_3CH_2O, $^3J_{POCC}$ 5.98), 16.37 (d, CH_3CH_2O,

Downloaded At: 18:36 28 January 2011

$^3J_{POCC}$ 5.91), 51.12 (d, $NHCH_2$, $^3J_{PCNC}$ 17.30), 56.01 (s, CH_3Ox3), 59.60 (d, P-CH, $^1J_{PC}$ 154.10), 62.69 (d, CH_3CH_2O, $^2J_{POC}$ 7.11), 62.84 (d, CH_3CH_2O, $^2J_{POC}$ 7.36), 105.47 (s, C-ortho of trimethoxybenzyl ring), 105.57 (s, C-ortho of trimethoxybenzyl ring), 126.90–128.36 (aromatic envelope), 131.06 (C-meta of trimethoxybenzyl ring), 131.12 (C-meta of trimethoxybenzyl ring), 137.49 (C-para of trimethoxybenzyl ring), 139.21 (s, CH_2Cq), 153.10 (d, P-CHCq, $^2J_{PCC}$ 1.89); $^{31}P(CDCl_3)$: δ 24.09; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 424.1882. $C_{21}H_{31}NO_6P$ requires 424.1889. $[M + H - (CH_3CH_2O)_2P(O)H]^+$ 286.1449. $C_{17}H_{20}NO_3$ requires 286.1443.

O,O-Diphenyl 1-benzylamino 3',4',5'-trimethoxybenzylphosphonate (15)

(**3**, R′ = C_6H_5, R = 3,4,5-$(CH_3O)_3C_6H_2$) C,H,N (Found: C, 67.40; H, 5.65; N, 2.42. Calc. for $C_{26}H_{30}NO_6P$: C, 67.05; H, 5.78; N, 2.70%); $^1H(CDCl_3)$: δ 3.67 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.37), 3.92 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.12), 3.78 (s, 9H, CH_3Ox3), 4.30 (d, 1H, P-CH, $^2J_{PCH}$ 19.80), 6.70 (s, 1H, H-ortho trimethoxybenzylphosphonate ring), 6.71 (s, 1H, H-ortho trimethoxybenzylphosphonate ring), 6.88–7.36 (m, 15H, C_6H_5x3); $^{13}C(CDCl_3)$: δ 51.13 (d, $NHCH_2$, $^3J_{PCNC}$ 17.93), 56.10 (s, CH_3Ox3), 59.58 (d, P-CH, $^1J_{PC}$ 156.23), 105.92 (s, C-ortho trimethoxybenzylphosphonate ring), 106.03 (s, C-ortho trimethoxybenzylphosphonate ring), 125.37–130.03 (aromatic envelope), 150.41 (d, C_6H_5O, Cq, $^2J_{POC}$ 9.81), 150.57 (d, C_6H_5O, Cq, $^2J_{POC}$ 10.57), 153.39 (d, P-CHCq); $^{31}P(CDCl_3)$: δ 16.92; FAB acc.ms (3-NOBA): m/z(%) Found: $[M + H]^+$ 520.1886. $C_{29}H_{31}NO_6P$ requires 520.1889. $[M + H - (C_6H_5O)_2P(O)H]^+$ 286.1446. $C_{17}H_{20}NO_3$ requires 286.1443.

O,O-Dimethyl 1-benzylamino 4'-fluorobenzylphosphonate (16)

(**3**, R′ = CH_3O, R = 4-FC_6H_4) C,H,N (Found: C, 59.56; H, 6.12; N, 4.16. Calc. for $C_{16}FH_{19}NO_3P$: C, 59.44; H, 5.88; N, 4.33%); $^1H(CDCl_3)$: δ 2.40 (br, s, 1H, $NHCH_2$), 3.52 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 14.34), 3.79 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.32), 3.57 (d, 3H, CH_3O, $^3J_{POCH}$ 10.49), 3.73 (d, 3H, CH_3O, $^3J_{POCH}$ 10.52), 4.04 (d, 1H, P-CH, $^2J_{PCH}$ 19.89), 7.04–7.44 (m, 9H, aromatic envelope); $^{13}C(CDCl_3)$: δ 51.04 (d, $NHCH_2$, $^3J_{PCNC}$ 17.30), 53.40 (d, CH_3O, $^2J_{POC}$ 6.42), 53.71 (d, CH_3O, $^2J_{POC}$ 7.04), 58.43 (d, P-CH, $^1J_{PC}$ 155.04), 125.36–131.23 (aromatic envelope), 138.95 (s, CH_2Cq), 162.49 (d, C_4-F, $^1J_{FC}$ 246.36); $^{31}P(CDCl_3)$: δ 26.20 (d); $^{19}F(CDCl_3)$: δ −114.70 to −114.56; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 324.1168. $C_{16}FH_{20}NO_3P$ requires 324.1165. $[M + H - (CH_3O)_2P(O)H]^+$ 214.1035. $C_{14}FH_{13}N$ requires 214.1032.

Downloaded At: 18:36 28 January 2011

***O,O-Diethyl 1-benzylamino 4'-fluorobenzylphosphonate* (17)**

(**3**, R′ = CH_3CH_2, 4-FC_6H_4) C,H,N (Found: C, 61.86; H, 6.70; N, 3.97. Calc. for $C_{18}FH_{23}NO_3P$: C, 61.54; H, 6.55; N, 3.99%); $^1H(CDCl_3)$: δ 1.15 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.07), 1.27 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.08), 2.20 (s, br, 1H, $NHCH_2$), 3.52 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.37), 3.79 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.42), 4.04–4.20 (m, 4H, CH_3CH_2Ox2), 7.03–7.81 (m, 9H, C_6H_5 overlapping H_2, H_3, H_5, H_6 of fluorobenzylphosphonate ring); $^{13}C(CDCl_3)$: δ 16.27 (d, CH_3CH_2O, $^3J_{POCC}$ 6.29), 16.38 (d, CH_3CH_2O, $^3J_{POCC}$ 6.73), 51.11 (d, $NHCH_2$, $^3J_{PCNC}$ 17.42), 58.78 (d, P-CH, $^1J_{PC}$ 154.60), 62.80 (d, CH_3CH_2O, $^2J_{POC}$ 6.86), 62.97 (d, CH_3CH_2O, $^2J_{POC}$ 7.11), 125.21–160.46 (aromatic envelope), 164.32 (d, C_4-F, $^1J_{FC}$ 250.89); $^{31}P(CDCl_3)$: δ 23.93 (d); $^{19}F(CDCl_3)$: δ −110.05 to −109.02 (m); FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 352.1475. $C_{18}FH_{24}NO_3P$ requires 352.1478. $[M + H - (CH_3CH_2O)_2P(O)H]^+$ 214.1034. $C_{14}FH_{13}N$ requires 214.1032.

***O,O-Dibenzyl 1-benzylamino 4'-fluorobenzylphosphonate* (18)**

(**3**, R′ = $C_6H_5CH_2$, R = 4-FC_6H_4) C,H,N (Found: C, 70.44, H, 5.80, N, 2.92. Calc. for $C_{28}FH_{27}NO_3P$: C, 70.74, H, 5.68, N, 2.95%); $^1H(CDCl_3)$: δ 2.56 (s, 1H, $NHCH_2$), 3.48 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.30), 3.76 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.19), 4.04 (d, 1H, P-CH, $^2J_{PCH}$ 19.87), 4.74–4.86 (m, 2H, $C_6H_5CH_2$), 4.88–5.10 (m, 2H, $C_6H_5CH_2$), 6.97–7.36 (m, 19H, aromatic envelope); $^{13}C(CDCl_3)$: δ 51.13 (d, $NHCH_2$, $^3J_{PCNC}$ 17.36), 59.05 (d, P-CH, $^1J_{PC}$ 154.66), 68.10 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 6.92), 68.41 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 6.98), 125.27–136.16 (aromatic envelope), 139.01 (s, P-CHCq), 160.52 (d, P-CHCq, $^2J_{PCC}$ 4.72); $^{31}P(CDCl_3)$: δ 24.79 (d); $^{19}F(CDCl_3)$: δ −114.77 to −114.63; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 476.1795. $C_{28}FH_{28}NO_3P$ requires 476.1791. $[M + H - (C_6H_5CH_2O)_2P(O)H]^+$ 214.1034. $C_{14}FH_{13}N$ requires 214.103.

***O,O-Dimethyl 1-benzylamino 4'-trifluoromethylbenzylphosphonate* (19)**

(**3**, R′ = CH_3, R = 4-$CF_3C_6H_4$) C,H,N (Found: C, 54.31; H, 5.03; N, 3.57. Calc. for $C_{17}F_3H_{19}NO_3P$: C, 54.69; H, 5.09; N, 3.75%); $^1H(CDCl_3)$: δ 3.54 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.45), 3.60 (d, 3H, CH_3O, $^3J_{POCH}$ 10.88), 3.74 (d, 3H, CH_3O, $^3J_{POCH}$ 10.91), 3.81 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.51), 4.15 (d, 1H, P-CH, $^2J_{PCH}$ 20.22), 7.20–7.36 (m, 5H, C_6H_5), 7.56 (d, 2H, H_3, H_5 of benzylphosphonate ring, $^3J_{HCCH}$ 8.81), 7.63 (d, 2H, H_2, H_6 of benzylphosphonate

Downloaded At: 18:36 28 January 2011

ring, $^3J_{HCCH}$ 8.82); $^{13}C(CDCl_3)$: δ 51.18 (d, $NHCH_2$, $^3J_{PCNC}$ 17.11), 53.41 (d, CH_3O, $^2J_{POC}$ 6.67), 53.74 (d, CH_3O, $^2J_{POC}$ 7.04), 58.86 (d, P-CH, $^1J_{PC}$ 152.90), 125.38–130.37 (aromatic envelope), 130.61 (s, CH_2Cq), 139.82 (d, P-CHCq, $^2J_{PCC}$ 3.71); $^{31}P(CDCl_3)$: δ 25.44; $^{19}F(CDCl_3)$: δ −63.03 (d); FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 374.1135. $C_{17}F_3H_{20}NO_3P$ requires 374.1133. $[M + H - (CH_3O)_2P(O)H]^+$ 264.1003. $C_{15}F_3H_{13}N$ requires 264.1000.

O,O-Diethyl 1-benzylamino 4'-trifluoromethylbenzylphosphonate (20)

(**3**, R′ = CH_3CH_2, R = 4-$CH_3C_6H_4$) C,H,N (Found: C, 57.13; H, 5.77; N, 3.53. Calc. for $C_{19}F_3H_{23}NO_3P$: C, 56.86; H, 5.74; N, 3.49%); $^1H(CDCl_3)$: δ 1.17 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.04), 1.28 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.06), 2.36 (s, br, 1H, $NHCH_2$), 3.52 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.34), 3.80 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.32), 4.01–4.19 (m, 4H, CH_3CH_2Ox2), 7.23–7.68 (m, 9H, aromatic envelope); $^{13}C(CDCl_3)$: δ 16.66 (d, CH_3CH_2O, $^3J_{POCC}$ 5.67), 16.80 (d, CH_3CH_2O, $^3J_{POCC}$ 5.83), 51.76 (d, $NHCH_2$, $^3J_{PCNC}$ 17.16), 59.75 (d, P-CH, $^1J_{PC}$ 152.14), 63.35 (d, CH_3CH_2O, $^2J_{POC}$ 6.84), 63.53 (d, CH_3CH_2O, $^2J_{POC}$ 6.95), 125.74–129.42 (aromatic envelope), 139.28 (s, P-CHCq); $^{31}P(CDCl_3)$: δ 23.14; $^{19}F(CDCl_3)$: δ—62.95 (d); FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 402.1443. $C_{19}F_3H_{24}NO_3P$ requires 402.1446. $[M + H—(CH_3CH_2O)_2P(O)H]^+$ 264.1002. $C_{15}F_3H_{13}N$ requires 264.1000.

O,O-Dibenzyl 1-benzylamino 4'-trifluoromethylbenzylphosphonate (21)

(**3**, R′ = $C_6H_5CH_2$, R = 4-$CF_3C_6H_4$) C,H,N (Found: C, 66.49; H, 5.05; N, 2.55. Calc. for $C_{29}F_3H_{27}NO_3P$: C, 66.29; H, 5.14; N, 2.67%); $^1H(CDCl_3)$: δ 3.53 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.43), 3.81 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.43), 4.18 (d, 1H, P-CH, $^2J_{PCH}$ 20.21), 4.90–5.16 (m, 4H, $C_6H_5CH_2Ox2$), 7.16–7.48 (m, 15H, C_6H_5x3), 7.53 (d, H_2, H_6 of benzylphosphonate ring, $^3J_{HCCH}$ 8.66), 7.62 (d, H_3, H_5 of benzylphosphonate ring, $^3J_{HCCH}$ 8.64); $^{13}C(CDCl_3)$: δ 51.33 (d, $NHCH_2$, $^3J_{PCNC}$ 17.23), 59.57 (d, P-CH, $^1J_{PC}$ 152.77), 68.24 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 6.79), 68.59 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 7.04), 125.40–129.87 (aromatic envelope), 135.90 (d, $C_6H_5CH_2O$-Cq, $^3J_{POCC}$ 5.85), 136.12 (d, $C_6H_5CH_2O$-Cq, $^3J_{POCC}$ 5.98), 139.83 (s, P-CHCq); $^{31}P(CDCl_3)$: δ 24.14; $^{19}F(CDCl_3)$: δ −62.88 (d); FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 526.1756. $C_{29}F_3H_{28}NO_3P$ requires 526.1759. $[M + H—(C_6H_5CH_2O)_2P(O)H]^+$ 264.1003. $C_{15}F_3H_{13}N$ requires 264.1000.

Downloaded At: 18:36 28 January 2011

***O,O-Dimethyl 1-benzylamino 4'-dimethylaminobenzylphosphonate* (22)**

(**3**, R′ = CH_3, R = 4-$(CH_3)_3NC_6H_4$), C,H,N (Found: C, 62.28; H, 7.27; N, 8.12. Calc. for $C_{18}H_{25}N_2O_3P$: C, 62.07; H, 7.18; N, 8.05%); ^{1}H($CDCl_3$): δ 2.50 (s, br, 1H, $NHCH_2$), 2.88 (s, 6H, $N(CH_3)_2$), 3.51 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 12.97), 3.77 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.14), 3.47 (d, 3H, CH_3O, $^3J_{POCH}$ 10.40), 3.69 (d, 3H, CH_3O, $^3J_{POCH}$ 10.44), 3.92 (d, 1H, P-CH, $^2J_{PCH}$ 19.48), 6.69 (d, 2H, H-ortho of dimethylaminobenzyl ring, $^3J_{HCCH}$ 8.55), 7.23 (m, 7H, aromatic envelope); ^{13}C($CDCl_3$): δ 39.75 (s, $N(CH_3)_2$), 50.26 (d, $NHCH_2$, $^3J_{PCNC}$ 17.42), 52.66 (d, CH_3O, $^2J_{POC}$ 6.98), 52.90 (d, CH_3O, $^2J_{POC}$ 7.11), 57.86 (d, P-CH, $^1J_{PC}$ 156.23), 111.80–128.83 (aromatic envelope), 138.92 (C_4-N), 149.70 (d, P-CHCq, $^2J_{PCC}$ 1.57); ^{31}P($CDCl_3$): δ 27.15; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 349.1683. $C_{18}H_{26}N_2O_3P$ requires 349.1681. $[M + H—(CH_3O)_2P(O)H]^+$ 239.1550. $C_{16}H_{19}N_2$ requires 239.1548.

***O,O-Diethyl 1-benzylamino 4'-dimethylaminobenzylphosphonate* (23)**

(**3**, R′ = CH_3CH_2, R = 4-$(CH_3)_2NC_6H_4$) C,H,N (Found: C, 63.65; H, 7.76; N, 7.36. Calc. for $C_{20}H_{29}N_2O_3P$: C, 63.83; H, 7.71; N, 7.45%); ^{1}H($CDCl_3$): δ 1.10 (t, 3H, CH_3CH_2, $^3J_{HCCH}$ 7.06), 1.25 (t, 3H, CH_3CH_2, $^3J_{HCCH}$ 7.07), 2.30 (s, br, 1H, $NHCH_2$), 2.88 (s, 6H, $N(CH_3)_2$), 3.52 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.30), 3.78 (d, 1H, $NHCH_2$ gem $^2J_{HCH}$ 13.25), 3.90 (d, 1H, P-CH, $^2J_{PCH}$ 19.27), 4.00–4.14 (m, 4H, CH_3CH_2Ox2), 6.69 (d, 2H, H_2, H_6 of dimethylaminobenzylphosphonate ring, $^3J_{HCCH}$ 8.61), 7.17–7.29 (m, 7H, C_6H_5 overlapping H_3, H_5 of dimethylaminobenzylphosphonate ring); ^{13}C($CDCl_3$): δ 16.74 (d, CH_3CH_2O, $^3J_{POCC}$ 5.73), 16.90 (d, CH_3CH_2O, $^3J_{POCC}$ 5.80), 40.90 (s, $N(CH_3)_2$), 51.31 (d, $NHCH_2$, $^3J_{PCNC}$ 17.62), 59.11 (d, P-CH, $^1J_{PC}$ 155.82), 63.09 (d, CH_3CH_2O, $^2J_{POC}$ 7.06), 63.19 (d, CH_3CH_2O, $^2J_{POC}$ 7.11), 123.01 (d, Cq of benzylamino ring, $^4J_{PC}$ 4.08), 127.40–129.89 (aromatic envelope), 139.92 (s, C_4-$N(CH_3)_2$), 150.65 (d, P-C-Cq, $^2J_{PCC}$ 2.53); ^{31}P($CDCl_3$): δ 24.93; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 377.1990. $C_{20}H_{30}N_2O_3P$ requires 377.1994. $[M + H - (CH_3CH_2O)_2P(O)H]^+$ 239.1550. $C_{16}H_{19}N_2$ requires 239.1548.

***O,O-Dibenzyl 1-benzylamino 4'-dimethylaminobenzylphosphonate* (24)**

(**3**, R′ = $C_6H_5CH_2$, R = 4-$(CH_3)_2NC_6H_4$) C,H,N (Found: C, 72.38; H, 6.39; N, 5.32. Calc. for $C_{30}H_{33}N_2O_3P$: C, 72.00; H, 6.60; N, 5.60%); ^{1}H($CDCl_3$): δ 3.00 (s, 6H, $N(CH_3)_2$), 3.61 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.66), 3.86 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.67), 4.09 (d, 1H, P-CH, $^2J_{PCH}$), 4.73–5.20 (m, 4H, $C_6H_5CH_2Ox2$),

Downloaded At: 18:36 28 January 2011

6.82 (d, 2H, H_2, H_3 of dimethylaminobenzylphosphonate ring, $^3J_{HCCH}$), 7.25–7.45 (m, 7H, C_6H_5 overlapping H_3, H_5 of dimethylaminobenzylphosphonate ring); $^{13}C(CDCl_3)$: δ 40.26 (s, $N(CH_3)_2$), 50.70 (d, NHCH2, $^3J_{PCNC}$ 17.80), 58.78 (d, P-CH, $^1J_{PC}$ 156.23), 67.71 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 6.92), 67.97 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 6.98), 125.76–141.71 (aromatic envelope), 150.14 (d, P-CHCq, $^2J_{PCC}$ 1.76); $^{31}P(CDCl_3)$: δ 25.92; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 501.2303. $C_{30}H_{34}N_2O_3P$ requires 501.2307. $[M + H - (C_6H_5CH_2O)_2P(O)H]^+$ 239.1550. $C_{16}H_{19}N_2$ requires 239.1548.

O,O-Dimethyl 1-benzylamino 4'-chlorobenzylphosphonate (25)

(**3**, R′ = CH_3, R = 4-ClC_6H_4) C,H,N (Found: C, 56.29; H, 5.34; N, 3.79. Calc. for $C_{16}H_{19}NO_3PCl$: C, 56.64; H, 5.61; N, 4.13%); $^1H(CDCl_3)$: δ 2.51 (s, br, 1H, $NHCH_2$), 3.51 (d, 1H, $NHCH_2$ gem $^2J_{HCH}$ 13.29), 3.58 (d, 3H, CH_3O, $^3J_{POCH}$ 10.38), 3.73 (d, 3H, CH_3O, $^3J_{POCH}$ 10.45), 3.79 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.32), 4.03 (d, 1H, P-CH, $^2J_{PCH}$ 20.19), 7.22–7.35 (m, 4H, H_2, H_3, H_5, H_6 of chlorobenzylphosphonate ring), 7.36 (s, 5H, C_6H_5); $^{13}C(CDCl_3)$: δ 51.34 (d, $NHCH_2$, $^3J_{PCNC}$ 17.32), 53.76 (d, CH_3O, $^2J_{POC}$ 7.21), 54.06 (d, CH_3O, $^2J_{POC}$ 6.97). 58.79 (d, P-CH, $^1J_{PC}$ 154.22), 127.56–139.05 (aromatic envelope); $^{31}P(CDCl_3)$: δ 25.99; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 340.0265. $C_{16}H_{20}NO_3PCl$ requires 340.0269. $[M + H - (CH_3O)_2P(O)H]^+$ 230.0733. $C_{14}H_{13}NCl$ requires 230.0737.

O,O-Diethyl 1-benzylamino 4'-chlorobenzylphosphonate (26)

(**3**, R′ = CH_3CH_2, R = 4-ClC_6H_4) C,H,N (Found: C, 58.59; H, 6.47; N, 3.58. Calc. for $C_{18}H_{23}NO_3PCl$: C, 58.86; H, 6.23; N, 3.82%); $^1H(CDCl_3)$: δ 1.17 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.08), 1.27 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.06), 2.21 (s, br, 1H, $NHCH_2$), 3.51 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.35), 3.79 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.34), 4.00 (d, 1H, P-CH, $^2J_{PCH}$ 20.36), 4.11–4.19 (m, 4H, CH_3CH_2Ox2), 7.22–7.39 (m, 9H, H_2, H_3, H_5, H_6 of chlorobenzylphosphonate ring overlapping C_6H_5); $^{13}C(CDCl_3)$: δ 16.33 (d, CH_3CH_2O, $^3J_{POCC}$ 5.95), 16.43 (d, CH_3CH_2O, $^3J_{POCC}$ 6.11), 51.18 (d, NHCH2, $^3J_{PCNC}$ 17.20), 58.93 (d, P-CH, $^1J_{PC}$ 153.53), 62.89 (d, CH_3CH_2O, $^2J_{POC}$ 6.84), 63.05 (d, CH_3CH_2O, $^2J_{POC}$ 7.26), 127.08–160.56 (aromatic envelope); $^{31}P(CDCl_3)$: δ 23.58; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 368.1180. $C_{18}H_{24}NO_3PCl$ requires 368.1182. $[M + H - (CH_3CH_2O)_2P(O)H]^+$ 230.0734. $C_{14}H_{13}NCl$ requires 230.0737.

Downloaded At: 18:36 28 January 2011

***O,O-Diisopropyl 1-benzylamino 4'-chlorobenzylphosphonate* (27)**

(**3**, R′ = $(CH_3)_2CH$, R = 4-ClC_6H_4) C,H,N (Found: C, 60.41; H, 6.83; N, 3.36. Calc. for $C_{20}H_{27}NO_3PCl$: C, 60.76; H, 6.84; N, 3.54%); $^1H(CDCl_3)$: δ 1.23–1.28 (m, 12H, $(CH_3)_2CHOx2$), 2.55 (s, br, 1H, $NHCH_2$), 3.50 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.29), 3.78 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.31), 3.93 (d, 1H, P-CH, $^2J_{PCH}$ 20.29), 4.50–4.58 (m, 1H, $(CH_3)_2CHO$), 4.26–4.76 (m, 1H, $(CH_3)_2CHO$), 7.22–7.44 (m, 9H, H_2, H_3, H_5, H_6 of chlorobenzylphosphonate ring overlapping C_6H_5); $^{13}C(CDCl_3)$: δ 23.51 (d, $(CH_3)_2CHO$, $^3J_{POCC}$ 5.62), 23.90 (d, $(CH_3)_2CHO$, $^3J_{POCC}$ 5.60), 51.26 (d, $NHCH_2$, $^3J_{PCNC}$ 17.54), 59.44 (d, P-CH, $^1J_{PC}$ 155.36), 71.42 (d, $(CH_3)_2CHO$, $^2J_{POC}$ 7.12), 71.49 (d, $(CH_3)_2CHO$, $^2J_{POC}$ 7.27), 127.04–160.53 (aromatic envelope); $^{31}P(CDCl_3)$: δ 21.87; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 396.1492. $C_{20}H_{28}NO_3PCl$ requires 396.1495. $[M + H - ((CH_3)_2CHO)_2P(O)H]^+$ 230.0733. $C_{14}H_{13}NCl$ requires 230.0737.

Downloaded At: 18:36 28 January 2011

***O,O-Diphenyl 1-benzylamino 4'-chlorobenzylphosphonate* (28)**

(**3**, R′ = C_6H_5, R = 4-ClC_6H_4) C,H,N (Found: C, 67.19; H, 5.15; N, 2.73. Calc. for $C_{26}H_{23}NO_3PCl$: C, 67.39; H, 4.97; N, 3.02%); $^1H(CDCl_3)$: δ 2.49 (s, br, 1H, $NHCH_2$), 3.59 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.31), 3.87 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.29), 4.35 (d, 1H, P-CH, $^2J_{PCH}$ 20.05), 6.90–7.49 (m, 19H, H_2, H_3, H_5, H_6 overlapping C_6H_5Ox3); $^{13}C(CDCl_3)$: δ 51.44 (d, NHCH2, $^3J_{PCNC}$ 18.11), 59.04 (d, P-CH, $^1J_{PC}$ 157.37), 125.76–161.03 (aromatic envelope); $^{31}P(CDCl_3)$: δ 16.50; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 464.1185. $C_{26}H_{23}NO_3PCl$ requires 464.1182. $[M + H - (C_6H_5O)_2P(O)H]^+$ 230.0734. $C_{14}H_{13}NCl$ requires 230.0737.

***O,O-Dibenzyl 1-benzylamino 4'-chlorobenzylphosphonate* (29)**

(**3**, R′ = $C_6H_5CH_2$, R = 4-ClC_6H_5) C,H,N (Found: C, 68.72; H, 5.67; N, 2.87. Calc. for $C_{28}H_{27}NO_3PCl$: C, 68.43; H, 5.50; N, 2.85%); $^1H(CDCl_3)$: δ 2.46 (s, br, 1H, $NHCH_2$), 3.46 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.33), 3.74 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.35), 4.02 (d, 1H, P-CH, $^2J_{PCH}$ 20.16), 4.71–4.95 (m; 2H, $C_6H_5CH_2$), 4.96–5.08 (m, 2H, $C_6H_5CH_2$), 7.07–7.33 (m, 19H, H_2, H_3, H_5, H_6 overlapping C_6H_5Ox3); $^{13}C(CDCl_3)$: δ 51.44 (d, $NHCH_2$, $^3J_{PCNC}$ 17.35), 59.43 (d, P-CH, $^1J_{PC}$ 154.18), 68.45 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 7.12), 68.76 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 7.27), 127.20–160.88 (aromatic envelope); $^{31}P(CDCl_3)$: δ 24.50; FAB

acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 492.1498. $C_{28}H_{28}NO_3PCl$ requires 492.1495. $[M + H - (C_6H_5CH_2O)_2P(O)H]^+$ 230.0734. $C_{14}H_{13}NCl$ requires 230.0737.

O,O-Diethyl 1-benzylaminopentafluorobenzylphosphonate (30)

(**3**, R′ = CH_3CH_2, R = C_6F_5) C,H,N (Found: C, 51.36; H, 4.12; N, 3.66. Calc. for $C_{18}F_5H_{19}NO_3P$: C, 51.06; H, 4.49; N, 3.31%); $^1H(CDCl_3)$: δ 1.24 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.06), 1.33 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.17), 3.70 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.09), 3.88 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.14), 4.10–4.28 (m, 4H, CH_3CH_2Ox2), 4.44 (d, 1H, P-CH, $^2J_{PCH}$ 24.66), 7.15–7.42 (m, 5H, C_6H_5); $^{13}C(CDCl_3)$: δ 16.23 (d, CH_3CH_2O, $^3J_{POCC}$ 7.80), 16.77 (d, CH_3CH_2O, $^3J_{POCC}$ 7.74), 51.31 (d, P-CH, $^1J_{PC}$ 162.90), 52.83 (d, $NHCH_2$, $^3J_{PCNC}$ 16.09), 63.37 (d, CH_3CH_2O, $^2J_{POC}$ 7.16), 64.11 (d, CH_3CH_2O, $^2J_{POC}$ 7.01), 127.73–138.66 (aromatic envelope); $^{31}P(CDCl_3)$: δ 20.01; $^{19}F(CDCl_3)$: δ − 162.62 (m), −151.77 (m), −143.19 (m); FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 424.1111. $C_{18}F_5H_{20}NO_3P$ requires 424.1110. $[M + H - (CH_3CH_2O)_2P(O)H]$ 286.0661. $C_{14}F_5H_9N$ requires 286.0655.

O,O-Diisopropyl 1-benzylaminopentafluorobenzylphosphonate (31)

(**3**, R′ = $(CH_3)_2CH$, R = C_6F_5) C,H,N (Found: C, 53.48; H, 4.78; N, 3.02. Calc. for $C_{20}F_5H_{23}NO_3P$: C, 53.22; H, 5.10; N, 3.10%); $^1H(CDCl_3)$: δ 1.33 (d, 12H, $(CH_3)_2CHOx2$, $^3J_{HCCH}$ 6.17), 3.70 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.05), 3.87 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.02), 4.37 (d, 1H, P-CH, $^2J_{PCH}$ 24.86), 4.62–4.86 (m, 2H, $(CH_3)_2CHOx2$), 7.20–7.36 (m, 5H, C_6H_5); $^{13}C(CDCl_3)$: δ 23.76 (d, $(CH_3)_2CHO$, $^3J_{POCC}$ 5.46), 24.23 (d, $(CH_3)_2CHO$, $^3J_{POCC}$ 5.32), 51.77 (d, P-CH, $^1J_{PC}$ 164.58), 52.55 (d, $NHCH_2$, $^3J_{PCNC}$ 16.15), 71.73 (d, $(CH_3)_2CHO$, $^2J_{POC}$ 7.21), 72.44 (d, $(CH_3)_2CHO$, $^2J_{POC}$ 7.13), 127.27–138.81 (aromatic envelope); $^{31}P(CDCl_3)$: δ 18.31 (d); $^{19}F(CDCl_3)$: δ −162.51 (m), −155.18 (m), −143.14 (m); FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 452.1414. $C_{20}F_5H_{24}NO_3P$ requires 452.1414. $[M + H - ((CH_3)_2CHO)_2P(O)H]^+$ 286.0655. $C_{14}F_5H_9N$ requires 286.0655.

O,O-Di-n-butyl 1-benzylaminopentafluorobenzylphosphonate (32)

(**3**, R′ = $CH_3(CH_2)_3$, R = C_6F_5) C,H,N (Found: C, 55.48; H, 5.46; N, 2.96. Calc. for $C_{22}F_5H_{27}NO_3P$: C, 55.12; H, 5.64; N, 2.92%); $^1H(CDCl_3)$: δ 0.88 (t, 3H, terminal CH_3, $^3J_{HCCH}$ 7.38), 0.93 (t, 3H, terminal CH_3, $^3J_{HCCH}$ 7.37), 1.19–

Downloaded At: 18:36 28 January 2011

1.69 (m, 8H, $CH_2CH_2CH_2Ox2$), 3.70 (d, 1H, $NHCH_2$ gem $^2J_{HCH}$ 13.12), 3.88 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.06), 3.96–4.21 (m, 4H, CH_2Ox2), 4.60 (d, 1H, P-CH, $^2J_{PCH}$ 24.70), 7.15–7.41 (m, 5H, C_6H_5); $^{13}C(CDCl_3)$: δ 13.84 (s, terminal CH_3), 13.94 (s, terminal CH_3), 18.91 (s, CH_2CH_3), 19.04 (s, CH_2CH_3), 32.76 (d, $CH_2CH_2CH_3$, $^3J_{POCC}$ 6.23), 32.92 (d, $CH_2CH_2CH_3$, $^3J_{POCC}$ 5.93), 51.23 (d, P-CH, $^1J_{PC}$ 163.46), 52.80 (d, $NHCH_2$, $^3J_{PCNC}$ 16.13), 66.92 (d, CH_2O, $^2J_{POC}$ 7.50), 67.79 (d, CH_2O, $^2J_{POC}$ 6.92), 127.53–139.10 (aromatic envelope); $^{31}P(CDCl_3)$: δ 20.24; $^{19}F(CDCl_3)$: δ −162.27 (t), −154.91 (m), −142.58 (m); FAB acc.ms.(3-NOBA): m/z(%) Found: $[M + H]^+$ 480.1732. $C_{22}F_5H_{28}NO_3P$ requires 480.1727. $[M + H - (n\text{-}C_4H_9O)_2P(O)H]^+$ 286.0646. $C_{14}F_5H_9N$ requires 286.0655.

O,O-Diisopropyl 1-benzylamino 4'-bromobenzylphosphonate (33)

(**3**, R′ = $(CH_3)_2CH$, R = 4-BrC_6H_4) C,H,N (Found: C, 54.27; H, 5.94; N, 3.08. Calc. for $C_{20}H_{27}NO_3PBr$: C, 54.55; H, 6.14; N, 3.18%); $^1H(CDCl_3)$: δ 1.22–1.28 (m, 12H, $(CH_3)_2CHOx2$), 2.34 (s, br, 1H, $NHCH_2$), 3.50 (d, 1H, $NHC^H{}_2$, gem $^2J_{HCH}$ 13.31), 3.78 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.31), 3.92 (d, 1H, P-CH, $^2J_{PCH}$ 20.30), 4.50–4.58 (m, 1H, $(CH_3)_2CHO$), 4.62–4.72 (m, 1H, $(CH_3)_2CHO$), 7.22–7.33 (m, 7H, H_2, H_6 overlapped by C_6H_5), 7.48 (d, 2H, H_3, H_5 of bromobenzylphosphonate ring, $^3J_{HCCH}$); $^{13}C(CDCl_3)$: δ 23.50 (d, $(CH_3)_2CHO$, $^3J_{POCC}$ 5.58), 24.13 (d, $(CH_3)_2CHO$, $^3J_{POCC}$ 6.71), 51.25 (d, $NHCH_2$, $^3J_{PCNC}$ 17.34), 59.49 (d, P-CH, $^1J_{PC}$ 154.84), 71.39 (d, $(CH_3)_2CHO$, $^2J_{POC}$ 7.34), 71.41 (d, $(CH_3)_2CHO$, $^2J_{POC}$ 7.34), 121.54–139.10 (aromatic envelope); $^{31}P(CDCl_3)$: δ 21.68; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 440.0993. $C_{20}H_{28}NO_3PBr$ requires 440.0990. $[M + H - ((CH_3)_2CHO)_2P(O)H]^+$ 274.0234. $C_{14}H_{13}NBr$ requires 274.0231.

O,O-Diphenyl 1-benzylamino 4'-bromobenzylphosphonate (34)

(**3**, R′ = C_6H_5, R = 4-BrC_6H_4) C,H,N (Found: C, 61.31; H, 4.80; N, 2.52. Calc. for $C_{26}H_{23}NO_3PBr$: C, 61.41; H, 4.53; N, 2.76%); $^1H(CDCl_3)$: δ 2.48 (s, br, 1H, $NHCH_2$), 3.58 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.31), 3.85 (d, 1H, $NHCH_2$ gem $^2J_{HCH}$ 13.29), 4.33 (d, 1H, P-CH, $^2J_{PCH}$ 20.13), 6.90–7.50 (m, H_2, H_3, H_5, H_6 overlapped by C_6H_5Ox3); $^{13}C(CDCl_3)$: δ 51.63 (d, $NHCH_2$, $^3J_{PCNC}$ 18.13), 59.28 (d, P-CH, $^1J_{PC}$ 157.23), 126.00–161.32 (aromatic envelope); $^{31}P(CDCl_3)$: δ 16.38; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 508.0674. $C_{26}H_{24}NO_3PBr$ requires 508.0677. $[M + H—(C_6H_5O)_2P(O)H]^+$ 274.0234. $C_{14}H_{13}NBr$ requires 274.0231.

Downloaded At: 18:36 28 January 2011

***O,O-Diethyl 1-benzylamino 4'-carbomethoxybenzylphosphonate* (35)**

(**3**, R′ = CH_3CH_2, R = 4-$CH_3CO_2C_6H_4$) C,H,N (Found: C, 60.99; H, 6.94; N, 3.53. $C_{20}H_{26}NO_5P$ requires C, 61.38; N, 6.65; N, 3.58%); $^1H(CDCl_3)$: δ 1.15 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.06), 1.27 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.09), 3.52 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.32), 3.80 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.31), 3.91 (s, 3H, CH_3CO_2), P-CH, 4.10–4.18 (m, 4H, CH_3CH_2Ox2); $^{13}C(CDCl_3)$: δ 16.00 (CH_3CH_2Ox2), 51.71 (d, $NHCH_2$, $^3J_{PCNC}$ 17.22), 59.90 (d, P-CH, $^1J_{PC}$ 151.90), 63.32 (d, CH_3CH_2O, $^2J_{POC}$ 6.97), 63.49 (d, CH_3CH_2O, $^2J_{POC}$ 7.21), 127.51–167.23 (aromatic envelope); $^{31}P(CDCl_3)$: δ 23.19; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 392.1624. $C_{20}H_{27}NO_5P$ requires 392.1627. $[M + H—(CH_3CH_2O)_2P(O)H]^+$ 254.1184. $C_{16}H_{16}NO_2$ requires 254.1181.

***O,O-Diphenyl 1-benzylamino 4'-carbomethoxybenzylphosphonate* (36)**

(**3**, R′ = C_6H_5, R = 4-$CH_3CO_2C_6H_4$) C,H,N (Found: C, 68.58; H, 5.45; N, 2.75. $C_{28}H_{27}NO_5P$ requires C, 68.99; H, 5.34; N, 2.88%); $^1H(CDCl_3)$: δ 2.66 (s, br, 1H, $NHCH_2$), 3.56 (d, 1H, $NHCH_2$ gem $^2J_{HCH}$ 13.29), 3.84 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.39), 3.87 (s, CH_3CO_2), 4.41 (d, 1H, P-CH, $^2J_{PCH}$ 20.99), 6.79–7.82 (aromatic envelope); $^{13}C(CDCl_3)$: δ 51.39 (d, $NHCH_2$, $^3J_{PCNC}$ 18.22), 52.36 (s, CH_3CO_2), 59.35 (d, P-CH, $^1J_{PC}$ 156.20), 125.69–166.74 (aromatic envelope); $^{31}P(CDCl_3)$: δ 16.02; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 488.1624. $C_{28}H_{27}NO_5P$ requires 488.1627. $[M + H—(C_6H_5O)_2P(O)H]^+$ 254.1184. $C_{16}H_{16}NO_2$ requires 254.1181.

***O,O-Diethyl 1-benzylamino 3'-trifluoromethoxybenzylphosphonate* (37)**

(**3**, R′ = CH_3CH_2, R = 3-$CF_3OC_6H_4$) C,H,N (Found: C, 54.46; H, 5.57; N, 2.92. $C_{19}F_3H_{23}NO4P$ requires C, 54.68; H, 5.52; N, 3.36%); $^1H(CDCl_3)$: δ 1.16 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.06), 1.27 (t, 3H, CH_3CH_2O, $^3J_{HCCH}$ 7.05), 3.53 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.28), 3.81 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.28), 3.87–4.13 (m, 5H, CH_3CH_2Ox2) overlapping P-CH), 7.13–7.46 (m, 9H, C_6H_5 overlapping H_2, H_4, H_5, H_6 of phosphonate ring); $^{13}C(CDCl_3)$: δ 16.21 (d, CH_3CH_2O, $^3J_{POCC}$ 5.85), 16.37 (d, CH_3CH_2O, $^3J_{POCC}$ 6.07), 51.37 (d, $NHCH_2$, $^3J_{PCNC}$ 17.28), 59.25 (d, P-CH, $^1J_{PC}$ 152.75), 62.99 (d, CH_2O, $^2J_{POC}$ 6.83), 63.10 (d, CH_2O, $^2J_{POC}$ 7.30), 120.40–138.92 (aromatic envelope); $^{31}P(CDCl_3)$: δ 23.18; $^{19}F(CDCl_3)$: d −58.24 (s); FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 418.1392. $C_{19}F_3H_{24}NO_4P$ requires 418.1395. $[M + H—(CH_3CH_2O)_2P(O)H]^+$ 280.0945. $C_{15}F_3H_{13}NO$ requires 280.0949.

Downloaded At: 18:36 28 January 2011

***O,O-Diethyl 1-benzylamino 4-iminomethylpyridinephosphonate* (38)**

(**3**, R′ = CH_3, R = 4-NC_5H_5) ·C,H,N (Found: C, 58.48; H, 5.87; N, 9.47. $C_{15}H_{19}N_2O_3P$ requires C, 58.82; H, 6.21; N, 9.15%); ^{1}H($CDCl_3$): δ 3.55 (d, 3H, CH_3O, $^3J_{POCH}$ 10.65), 3.67 (d, 3H, CH_3O, $^3J_{POCH}$ 10.65), 3.98 (d, 1H, P-CH, $^2J_{PCH}$ 21.31), 3.22–3.50 (dd, 2H, $NHCH_2$, $^2J_{HCH}$), 7.00–8.68 (aromatic envelope); ^{13}C($CDCl_3$): δ 51.48 (d, $NHCH_2$, $^3J_{PCNC}$ 16.73), 52.90 (d, CH_3O, $^2J_{POC}$ 6.86), 58.65 (d, P-CH, $^1J_{PC}$ 151.83), 123.55–150.05 (aromatic envelope); ^{31}P($CDCl_3$): δ 24.78; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 307.1215. $C_{15}H_{20}N_2O_3P$ requires 307.1212. $[M + H—(CH_3O)_2P(O)H]^+$ 197.1079.$C_{13}H_{13}N_2$ requires 197.1079.

***O,O-Diethyl 1-benzylamino 4-iminomethylpyridinephosphonate* (39)**

(**3**, R′ = CH_3CH_2, R = 4-NC_5H_5) (Found: C, 61.37; H, 7.28; N, 7.96. $C_{17}H_{23}N_2O_3P$ requires C, 61.08; H, 6.89; N, 8.38%); ^{1}H($CDCl_3$): δ 1.09 (t, 3H, CH_3CH_2, $^3J_{HCCH}$ 7.03), 1.18 (t, 3H, CH_3CH_2, $^3J_{HCCH}$ 7.08), 3.44 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.36), 3.72 (d, 1H, $NHCH_2$, gem $^2J_{HCH}$ 13.36), 3.80–4.11 (m, 5H, CH_3CH_2Ox2 overlapping P-CH), 7.13–7.33 (m, 5H, C_6H_5), 8.51 (d, 2H, H_2, H_6, $^3J_{HCCH}$ 5.74), 8.58 (d, 2H, H_3, H_5, $^3J_{HCCH}$ 6.01); ^{13}C($CDCl_3$): δ 16.33 (d, CH_3CH_2O, $^3J_{POCC}$ 4.97), 16.20 (d, CH_3CH_2O, $^3J_{POCC}$ 5.91), 51.44 (d, $NHCH_2$, $^3J_{PCNC}$ 16.73), 58.91 (d, P-CH, $^1J_{PC}$ 150.64), 63.01 (d, CH_3CH_2O, $^2J_{POC}$ 6.98), 63.20 (d, CH_3CH_2O, $^2J_{POC}$ 7.04), 122.00–159.84 (aromatic envelope); ^{31}P($CDCl_3$): δ 22.40; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 335.1522. $C_{17}H_{24}N_2O_3P$ requires 335.1525. $[M + H—(CH_3CH_2O)_2P(O)H]^+$ 197.1074. $C_{13}H_{13}N_2$ requires 197.1079.

***O,O-Dibenzyl 1-benzylamino 4-iminomethylpyridinephosphonate* (40)**

(**3**, R′ = $C_6H_5CH_2$, R = 4-NC_5H_5) C,H,N (Found: C, 70.46; H, 6.36; N, 5.76. $C_{27}H_{27}N_2O_3P$ requires C, 70.59; H, 5.88; N, 6.10%); ^{1}H($CDCl_3$): δ 4.06 (d, 1H, P-CH, $^2J_{PCH}$ 21.94), 4.80–5.06 (m, 4H, $C_6H_5CH_2$Ox2), 7.05–7.43 (m, 15H, C_6H_5x3), 7.83 (d, 2H, H_2, H_6, $^3J_{HCCH}$ 5.03), 8.68 (d, 2H, H_3, H_5, $^3J_{HCCH}$ 6.53); ^{13}C($CDCl_3$): δ 53.29 (d, $NHCH_2$, $^3J_{PCNC}$ 13.15), 63.45 (d, P-CH, $^1J_{PC}$), 67.50 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 6.47), 68.39 (d, $C_6H_5CH_2O$, $^2J_{POC}$ 6.86), 123.67–163.26 (aromatic envelope); ^{31}P($CDCl_3$): δ 12.37; FAB acc.ms(3-NOBA): m/z(%) Found: $[M + H]^+$ 459.1835. $C_{27}H_{28}N_2O_3P$ requires 459.1838. $[M + H - (C_6H_5CH_2O)_2P(O)H]^+$ 197.1075. $C_{13}H_{13}N_2$ requires 197.1079.

Downloaded At: 18:36 28 January 2011

Acknowledgements

We would like to take this opportunity to thank the Mass Spectrometry Service, Dept. of Pharmaceutical Chemistry, The School of Pharmacy, University of London, for FAB mass spectral analyses. We also thank the Bruker AMX 400 University of London Intercollegiate Research Service for N.M.R. spectra. We thank Mr S. Boyer, A.C.L.S., University of North London for elemental analyses, and finally Prof. H. R. Hudson, A.C.L.S, Univeristy of North London, for helpful discussions. This work is sponsored by the Thrombosis Research Trust.

References

[1] D. Redmore, *Topics in Phosphorus Chemistry*, eds. E. J. Griffith and M. Grayson (John Wiley and Sons Inc., New York 1976).

[2] P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon*, **63**, 193 (1991); L. Cheng, C.A. Goodwin, M.F. Scully, V.V. Kakkar and G. Claeson, *Tetrahedron Letts.*, **32**(49), 7333 (1991); C. Wang, T.L. Taylor, A.J. Mical, S. Spitz and T.M. Reilly, *Tetrahedron Letts.*, **33(50)**, 7667 (1992); P. Hermann, I. Lukes, B. Maca and M. Budesinsky, *Phosphorus, Sulfur and Silicon*, **79**, 43.

[3] D. Green, G. Patel, S. Elgendy, J.A. Baban, G. Claeson, V.V. Kakkar and J. Deadman, *Tetrahedron*, **50(17)**, 5099 (1994).

[4] R. Chen and L. Mao, *Phosphorus, Sulfur and Silicon*, **89**, 97 (1994).

[5] G. Keglevich, I. Petnehazy, L. Toke and H.R. Hudson, *Phosphorus and Sulfur*, **29**, 341 (1987).

[6] H.R. Hudson, M. McPartlin, R.W. Matthews, H.R. Powell, R.O. Yusuf, Z.M. Jaszay, G. Keglevich, I. Petnehazy and L. Toke, *Phosphorus, Sulfur and Silicon*, **79**, 239 (1993).

[7] D.G. Cameron, C.S. Creaser, H.R. Hudson, M. Pianka and H. Wright, *Chemistry and Industry*, 774 (1984); C.S. Creaser, S. Crosland, H.R. Hudson, A. Kow, L. Powrozynk and O.O. Shode, *Org. Mass Spec.*, **23**, 148 (1988); D.G. Cameron, H.R. Hudson, I.A.O. Ojo, and M. Pianka, *Phosphorus and Sulfur*, **40**, 183 (1991); C. Yuan, S. Chen and G. Wang, *Phosphorus, Sulfur and Silicon*, **60**, 97 (1991).

[8] S.W.A. Bligh, N. Choi, D.St.C. Green, H.R. Hudson, C.M. McGrath, M. McPartlin and M. Pianka, *Polyhedron*, **12(23)**, 2887 (1993); S.W.A. Bligh, N. Choi, D.St.C. Green, H.R. Hudson, C. McGrath and M. Pianka, *Phosphorus, Sulfur and Silicon*, **111**, 49 (1996).

[9] D. Green, G. Patel, S. Elgendy, J.A. Baban, G. Claeson, V.V. Kakkar and J. Deadman, *Tetrahedron Letts.*, **34(43)**, 6917 (1993); A.S. Demir, C. Tanyeli, O. Sesenoglu, S. Demic, *Tetrahedron Letts.*, **37(3)**, 407 (1996).

[10] D. Green, G. Patel, S. Elgendy, J.A. Baban, E. Skordalakes, W. Husman, C.A. Goodwin, M.F. Scully, V.V. Kakkar and J. Deadman, *Phosphorus, Sulfur and Silicon*, **109–110**, 533 (1996).

Downloaded At: 18:36 28 January 2011