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Synthesis of Novel L-Phenylalanine Derivatives Substituted with a Keto Ylide as Stable Precursor of a Vicinal Tricarbonyl Moiety

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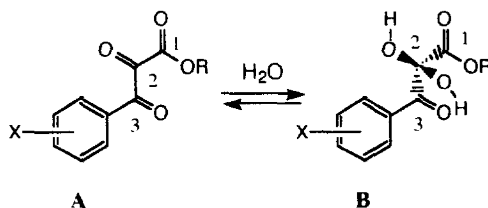
Abstract: Novel L-phenylalanine derivatives **5** containing a vicinal tricarbonyl moiety at the para position of the phenyl ring were prepared in 4 steps starting from N^{α}-Cbz-L-tyrosine benzyl ester. A 7 step reaction sequence lead to N^{α}-Fmoc protected derivatives **9** with the tricarbonyl structure masked as its stable keto ylide precursor, which is suitable for solid phase peptide synthesis. The phosphoranylidene intermediates **8** were transformed to the trioxo compounds **5** with Oxone® as oxidant Copyright © 1996 Elsevier Science Ltd

Vicinal tricarbonyl systems play a considerable role in the biological activity of natural products like the immunosuppressants FK506[1] and rapamycin[2] mimicking the twisted amide bond transition state that is essential to inhibition of the *cis-trans* peptidylprolyl isomerase.[3] Several peptidyl tricarbonyl derivatives have been shown to exhibit potent inhibition of hydrolytic enzymes such as serine proteases.[4] In addition, the vicinal tricarbonyl moiety offers a broad applicability towards the preparation of various natural products and their analogues.[5]

Protein-tyrosine phosphorylation by protein tyrosine kinases (PTKs), dephosphorylation by protein-tyrosine phosphatases (PTPases) on specific tyrosine residues, as well as the binding of proteins containing src homology 2 (SH2) domains to sequence-specific phosphotyrosine (pTyr)-containing proteins are crucial events of the cellular signal transduction. Specific inhibitors of these processes could be potential therapeutic agents for a variety of disease areas such as cancer.[6] In biological systems pTyr-containing compounds are of limited utility due to their hydrolytic lability to PTPases. Therefore, phosphonate analogues (CH_2-, CHF- and CF_2-phosphonates) have been widely explored as phosphatase stable mimics.[7] Poor cellular penetration due to the ionization of the phosphonate group at physiological pH is a major drawback of phosphonate-containing inhibitors.[8] Recently, non-phosphorus containing pTyr mimetics that utilize malonyl or 2-fluoromalonyl structure in place of the parent phosphate group were developed.[7b]

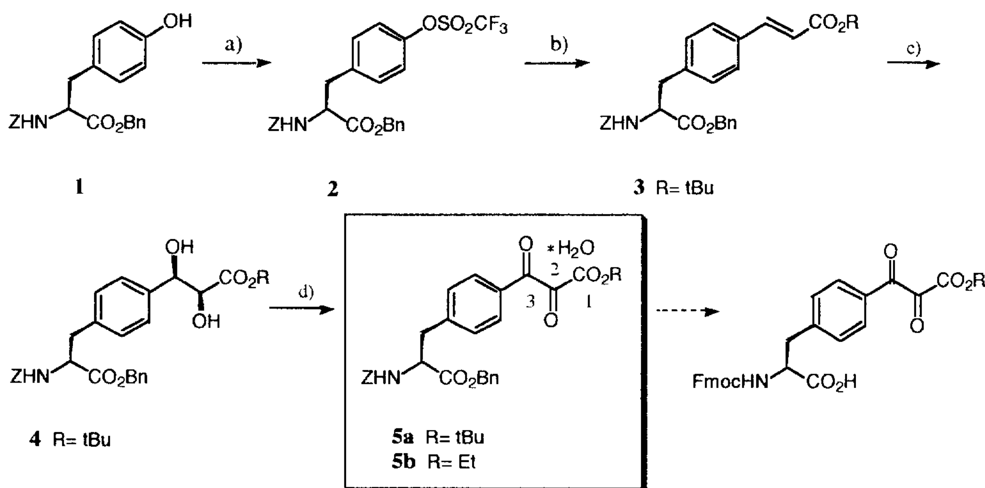
In the course on search for novel non-phosphorus based pTyr mimics for the preparation of signal transduction inhibitory compounds we examined by the highly electrophilic centre of the 1,2,3-tricarbonyl moiety for this purpose. The phenyl substituted compound **A** resembles in its hydrated form **B**[9] (Scheme 1) the tetrahedral centre of a phenyl phosphate or phosphonate moiety. Molecular modelling experiments suggest that the polar tricarbonyl moiety may occupy the phosphate binding pocket of for example SH2 domains[10] in a similar manner as the phosphonates and malonates mentioned above.[11] PTPase catalyzed protein dephosphorylation proceeds via the transient formation of a covalent thiophosphate linkage between the cystein moiety in the enzyme active site and the phosphate of tyrosine.[6c] The reactivity of the vicinal tricarbonyl functionality could lead to a covalent bond formation with the active site of the PTPases comparable to serine protease inhibition.[4]

Scheme 1



In this paper, we present two synthetic pathways towards novel L-phenylalanine derivatives substituted with a vicinal tricarbonyl moiety at the para position of the phenyl ring.[12] For the use in standard solid-phase peptide synthesis methodology based on Fmoc/ *tert*-butyl protection strategy, we kept the tricarbonyl structure masked as its stable keto ylide precursor.

Scheme 2

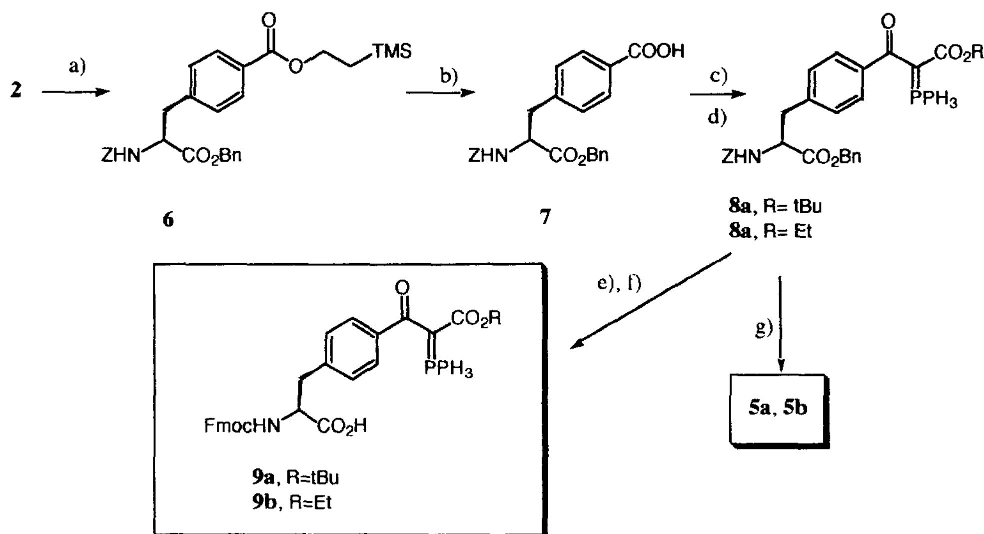


Reagents and conditions: (a) Phenyltriflimide, NEt_3, CH_2Cl_2, (91%); (b) *tert*-butylacrylate, $[(C_6H_5)_3P]_2PdCl_2$, NEt_3, DMF, 90°C, 24h, (81%); (c) 0.2M OsO_4 in THF, NMMO, acetone/ H_2O 8:1, rt, 24h, then aq. $Na_2S_2O_3$ (92%); (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, NEt_3, (87%).

Our efforts commenced with the preparation of triflate **2**[13] (m.p. 91-92°C) from commercially available N^{α}-Cbz-L-tyrosine benzyl ester **1** (Scheme 2), according to the procedure of Tilley *et al.*,[14] followed by the palladium (0)-catalyzed coupling with *tert*-butyl acrylate to give a 80.4% yield of crystalline **3**[13] (m.p. 107°C). Osmium-catalyzed *cis* hydroxylation of the olefin **3** in the presence of N-methylmorpholine (NMMO) afforded *cis*-diol **4**[13] (1:1 mixture of 2*S*, 3*R*- and 2*R*, 3*S*-diol) as a colorless oil.[15] Subsequent oxidation of **4** under Swern condition[16] smoothly provided the desired compound **5a**[17] in its hydrated form as confirmed by ^1H-, ^{13}C-NMR and mass spectrometric analysis. It turned out that the limited chemical stability of **5a**, which is due to the highly electrophilic centre of the vicinal tricarbonyl moiety, would cause problems during the protecting-group transformation to the final Fmoc-amino acid derivative and subsequent incorpoation into peptide sequences applying Fmoc/ *tert*-butyl chemistry. We therefore decided to prepare the amino acid through the stable phospharane precursor of the vicinal tricarbonyl moiety (Scheme 3).[18] This protected tricarbonyl moiety was proven to be fully compatible with solid phase peptide synthesis and would allow the release of the tricarbonyl after the peptide assembly by oxidative cleavage of the carbon-phosphorus double bond.[4,19]

Palladium(0) catalyzed alkoxycarbonylation of triflate **2** under an ambient CO atmosphere afforded the trimethylsilylethyl ester **6**[13] as an oil in 91% yield (Scheme 2).[20] Selective deprotection of the aryl ester group of **6** was achieved with 1.1 equivalents of tetrabutylammonium fluoride in dry THF to give acid **7**[13] as a white solid (m.p. 113-115°C) in 75% yield, which then was converted to the acid chloride by treatment with 1.2 equivalent of oxalyl chloride and catalytic DMF. The crude acid chloride was coupled with the respective ylides in the presence of the proton scavenger bis(trimethylsilyl)acetamide (BSA) to give the keto ylide intermediates (**8a** and **8b**[13], respectively).[18] Debenzylation of the keto ylides **8** was accomplished using standard hydrogenation conditions (H_2, Pd/C, EtOH) to afford the free amino acids which then were converted to the N^{α}-Fmoc protected amino acid **9a** and **9b**, respectively, with FmocOSu.[17]

Scheme 3



Reagents and conditions: (a) $Me_3SiCH_2CH_2OH$, $Pd(OAc)_2$, $(Ph_2PCH_2)_2CH_2$, NEt_3, (91%); (b) 1M nBu_4NF in THF, 4Å mol sieves, (75%); (c) $(COCl)_2$, toluene, cat. DMF, (quant.); (d) *tert*-butyl (triphenylphosphoranylidene)-acetate or ethyl (triphenylphosphoranylidene)acetate, BSA, toluene, (80 and 83%, resp.); (e) H_2, Pd/C, dioxane, (quant.); (f) Fmoc-OSu, 50% aq. MeCN, (quant.); (g) Oxone®, THF/ H_2O 2:1, 2h, (83%).

Following the procedure of Wasserman *et al.*[21], the phosphoranes **8a** and **8b** were oxidized with Oxone® in THF/H_2O at room temperature to give the tricarbonyl products **5a** and **5b**, respectively. Compound **5a** was identical with the product described in Scheme 1. The ^1H NMR spectum revealed a broad singulett at 5.25 ppm for the 2,2-diol, exchangeable with D_2O. The ^{13}C NMR chemical shift of the central carbon atom (C2) shows an upfield shift to 92 ppm which is in agreement with data from the literature.[22] The ^1H and ^{13}C NMR and MS analyses were consistent with the assigned structures and confirmed the existence of the hydrated form (**B**, Scheme 1).[17]

In summary, an efficient preparation of the N^{α}-Fmoc-L-phenylalanine derivatives **9** substituted with masked vicinal tricarbonyl moieties is described. The conversion of the phosphoranylidene intermediates **8** to the corresponding trioxo system **5** with Oxone® as oxidant could be demonstrated. Incorporation of the building blocks into peptide sequences by solid phase peptide synthesis and the subsequent release of the vicinal tricabonyl moiety under various oxidative conditions will be presented in the accompanying paper.

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17. Data for **5a**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.87 (d, J=8.4 Hz, 2H), 7.46-7.26 (m, 10H); 7.06 (d, J=8.4Hz, 2H); 5.25 (br.s, OH, exchangeable with D_2O); 5.24-5.05 (5H); 4.72 (dd, 1H-C(α)); 3.22 and 3.13 (dd, 1H-C(β) each); 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 192.5 (C-3); 171.0; 168.8; 155.5; 143.0; 136.0; 135.0; 130.2; 130.0; 129.8; 129.5; 129.0; 128.8; 128.6; 128.4; 91.5 (C-2); 84.4; 67.8; 67.2; 54.6; 38.2, 27.5. FAB MS (positive-ion mode, $C_{31}H_{31}NO_8$): 564 $[M+H_2O+H]^+$; 546 $[M+H]^+$. **5b**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (d, 2H); 7.40-7.25 (m, 10H); 7.07 (d, 2H); 5.25 (br.s, 2H, exchangable with D_2O); 5.20-5.05 (m, 5H); 4.72 (m, 1H); 4.20 (q, 2H); 3.22 and 3.12 (dd, 1H each); 1.07 (t, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 191.1 (C-3), 170.8; 169.9; 155.6; 143.3; 136.1; 134.8; 130.4; 130.3; 130.2; 129.9; 128.88, 128.82; 128.81; 128.67; 128.4; 128.2; 91.6 (C-2); 67.6; 67.2; 63.3;54.5; 38.3;13.8. FAB MS (positive-ion mode, $C_{29}H_{27}NO_8$): 536 $[M+H_2O+H]^+$; 518 $[M+H]^+$. Electrospray ionisation MS (ESI, negative-ion mode): 534 $[M+H_2O-H]^-$; 516 $[M-H]^-$. **9a**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.82-7.72 (m, 8H); 7.65-7.44 (m, 12H); 7.39-7.25 (m, 5H); 7.03 (d, J=8.3Hz, 2H); 5.74 (d, 1H-N); 4.55-4.51 (m, 1H-C(α)); 4.39-4.32 (m, 1H); 4.24-4.10 (m, 2H); 3.20 and 3.05 (dd, 1H-C(β) each); 0.97 (s, 9H). FAB-MS (positive-ion mode, $C_{49}H_{44}NO_7P$): 790 $[M+H]^+$. **9b**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.81-7.72 (m, 8H); 7.62-7.44 (m, 12H); 7.39-7.25 (m, 5H); 7.03 (d, J=8.0Hz, 2H); 5.73 (d, 1H-N); 4.58 (m, 1H-C(α)); 4.36 (m, 1H); 4.20 (m, 2H); 3.65 (q, J=7.0Hz, 2H); 3.20 and 3.04 (dd, 1H-C(β) each); 0.57 (t, J=7.0Hz, 3H). FAB-MS (positive-ion mode, $C_{47}H_{40}NO_7P$): 762 $[M+H]^+$.
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