Synthesis of Optically Active 2-(*tert*-Butyloxycarbonylamino)-4-dialkoxyphosphoryl-butanoate Protected Isosteres of *O*-Phosphonoserine for Peptide Synthesis

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The preparation of (*S*)-2-(*tert*-butoxycarbonylamino)-4-dialkoxyphosphorylbutanoate from (*S*)-aspartic acid is described.

Phosphonates are an important class of organic molecules[1] found extensively throughout biological systems. The enhanced chemical and enzymic stability of phosphonates has been utilized in the design of useful isosteric analogues of prototype phosphate molecules.[2,3] 2-Amino-4-phosphonobutyric acid, a naturally occurring glutamate analogue known to inhibit various enzyme processes[4,5] is a stable isosteric analogue of *O*-phosphonoserine. In our studies, we hoped to prepare stable peptide analogues of the highly phosphorylated regions of Human β-casein[6] by replacing *O*-phosphonoserine residues with the more stable 2-amino-4-phosphonobutyric acid residues. Subsequently we intended to use these peptide analogues as haptens to illicit Human β-casein specific monoclonal antibodies, which in turn might prove to be diagnostically useful.[7,8]

Previously reported approaches to the synthesis of 2-amino-4-phosphonobutyric acid, which afford D,L and optically enriched[9,10] preparations, were unsuitable for our purposes. We required a general route that would yield optically pure 2-amino-4-phosphonobutyric acid suitably protected at the amino and phosphonic acid functions to facilitate its use in existing solid and solution phase peptide[11] synthesis procedures.

Consequently, we have devised a synthetic route for the preparation of the appropriately protected (*S*)-2-(*tert*-butyloxycarbonylamino)-4-dialkoxyphosphorylbutanoic acids from inexpensive (*S*)-aspartic acid. The key transformation in the synthesis involves reaction of a protected aspartaldehyde derivative with dialkyl trimethylsilyl phosphites to give the corresponding 2-amino-4-(dialkoxyphosphoryl)-4-trimethylsilyloxybutanoic acid derivatives. This approach was favored over the classical Arbusov reaction,[12] since the reaction conditions are very mild and afford the product in high yield and chemical purity. The enantiomeric purity of the protected 2-amino-4-phosphonobutanoic acids was analysed using a HPLC modification of the Manning–Moore procedure[13] and was estimated at 99%.

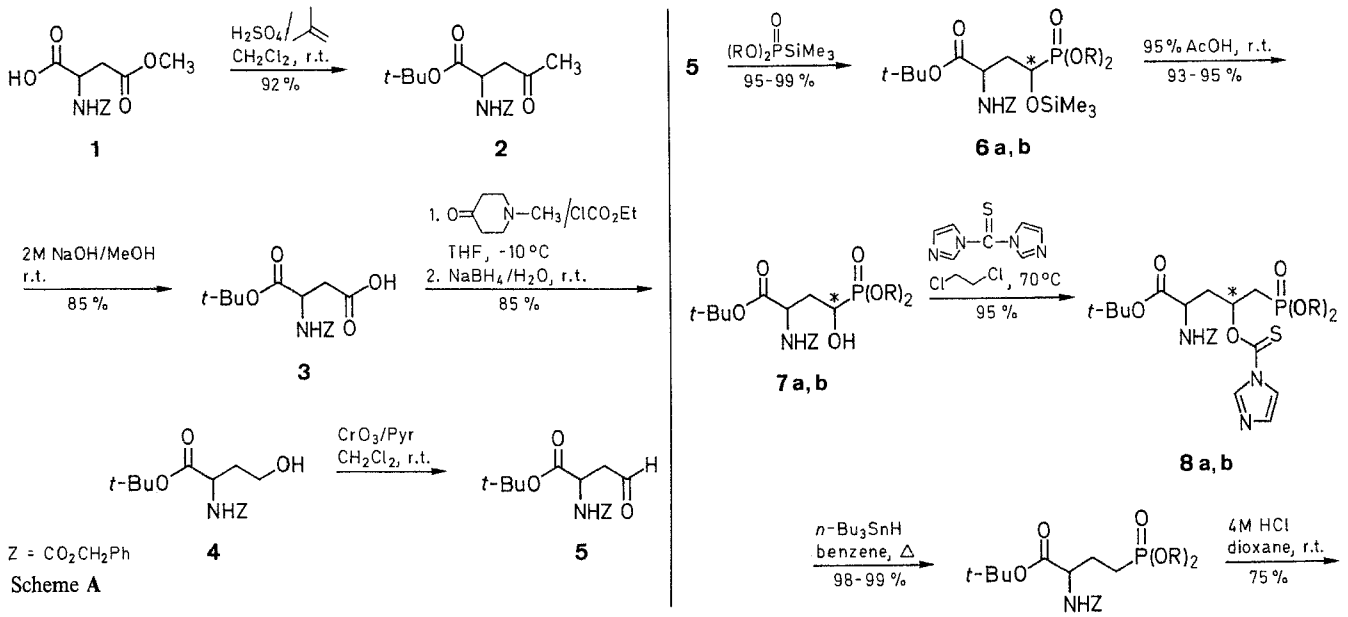
The key aspartaldehyde intermediate in this synthesis is conveniently prepared from an optically pure homoserine derivative. Protection of the α-amino and α-carboxylic acid functions of homoserine is sometimes complicated by the tendency of this γ-hydroxy amino acid to lactonize. We have found protected homoserine derivatives more accessible by reduction of the β-carboxyl group of appropriately protected (*S*)-aspartic acid derivatives.[14] This method allows the preparation of optically pure homoserine derivatives in gram quantities from readily available (*S*)-aspartic acid.

Hence, 4-methyl (*S*)-*N*-benzyloxycarbonylaspartate **(1)** was prepared in 72% overall yield from (*S*)-aspartic acid[15] (Scheme **A**). Reaction of **1** with isobutene[16] gives the α-*tert*-butyl ester **2** (Table 1) which upon treatment with 2 M sodium hydroxide in methanol affords 1-*tert*-butyl hydrogen (*S*)-*N*-benzyloxycarbonylaspartate **(3)** in 78% overall yield. Reduction of **3** via the mixed carbonic anhydride with sodium borohydride[14] provides *tert*-butyl (*S*)-*N*-benzyloxycarbonylhomoserinate **(4)** in 85% yield. The *tert*-butyl ester **4** is stable to storage at 4°C for indefinite periods with no evidence of lactone formation after 24 months.[17] Oxidation of the alcohol **4** with chromium(VI) oxide–pyridine in dichloromethane[18] affords (*S*)-*N*-benzyloxycarbonylaspartaldehyde *tert*-butyl ester **(5)** in 60% yield after column chromatography. Although reaction conditions were exhaustively optimized, the relatively low yield for this oxidation could not be improved and appeared to be caused by the formation of a side-product of unknown structure.

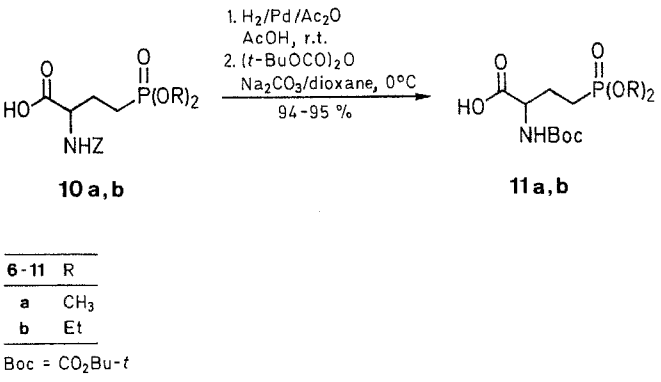
Table 1. Protected Aspartic Acid, Homoserine and Aspartaldehyde Derivatives **2–5** Prepared

Product[a]	Yield (%)	Molecular Formula[b]	$[\alpha]_D^{20}$ (*c*, EtOAc)	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ
2	92	$C_{17}H_{22}O_6$ (322.4)	−1.71° (1.75)	1.55 (s, 9H, *t*-C_4H_9); 2.88 (m, 2H, $CHCH_2$); 3.67 (s, 3H, CO_2CH_3; 4.51 (m, 1H, CH); 5.11 (s, 2H, CH_2Ar); 5.67 (br, 1H, NH); 7.17 (s, 5H_{arom})	27.8, 37.8, 51.0, 51.8, 66.9, 82.5, 128.1, 128.5, 136.5, 155.9, 169.5, 171.1
3	85	$C_{16}H_{20}O_6$ (308.3)	−0.9° (4.3)	1.42 (s, 9H, *t*-C_4H_9); 2.3–2.6 (m, 2H, $CHCH_2$); 4.2–4.35 (m, 1H, CH); 5.1 (s, 2H, CH_2Ar); 5.85 (d, 1H, NH, *J* = 8); 7.33 (s, 5H_{arom}); 9.42 (br s, 1H, CO_2H)	27.7, 36.5, 50.8, 67.1, 82.7, 128.1, 128.5, 131.1, s; 156.2, 169,5, 175.5
4	85	$C_{16}H_{22}O_5$ (294.4)	−14.0° (0.75)	1.45 (s, 9H, *t*-C_4H_9); 1.5–2.24 (m, 2H, $CHCH_2$); 3.25 (br, 1H, OH); 3.68 (m, 2H, CH_2OH); 4.36 (m, 1H, CH); 5.1 (s, 2H, CH_2Ar); 5.81 (d, 1H, NH, *J* = 5.7); 7.33 (s, 5H_{arom})	27.8, 35.4, 51.9, 58.4, 67.0, 82.1, 128.0, 128.4, 136.1, 156.7, 171.6
5	60	$C_{16}H_{20}O_5$ (292.3)	−9.1° (0.9)	1.43 (s, 9H, *t*-C_4H_9); 3.0 (d, 2H, CH_2CHO, *J* = 5.1); 4.53 (m, 1H, CH); 5.1 (s, 2H, CH_2Ar); 5.67 (d, 1H, NH, *J* = 5.7); 7.33 (s, 5H_{arom}); 9.7 (s, 1H, CHO)	27.8, 46.0, 49.7, 67.0, 82.8, 128.0, 128.5, 136.1, 155.9, 169,6, 199.1

[a] All compounds in Table 1 were homogeneous by TLC (silica gel).
[b] Satisfactory microanalyses obtained for **2** and **3**: C ±0.2, H ±0.22, N ±0.19. Compounds **4** and **5** were characterized by FAB-mass spectrometry: ^{19}**4** (+ve ions): 310[(M + 1)$^+$, 23%]; 210[(M + 1 − 100)$^+$, 100]; **5** (+ve ions): 308[(M + 1)$^+$, 10%]; 252[(M + 1 − 56)$^+$, 46].
[c] 100 MHz spectra.
[d] 25 MHz spectra.



Scheme A



Scheme B

Reaction of aldehyde **5** with dialkyl trimethylsilyl phosphites[21] (Scheme **B**) gives the corresponding 4-trimethylsilyloxy phosphonates **6** as a 1:1 mixture of *2S,4R*- and *2S,4S*- diastereoisomers in 95–99% yield after column chromatography (Table 2). Unexpectedly, the 4-trimethylsilyloxy group is stable to both treatment with aqueous methanol and chromatography on silica. The unusual stability of the 4-trimethylsilyloxy group is attributed to possible steric hindrance at the silicon atom by the phosphonate ester function, which might hinder hydrolysis of the silicon–oxygen bond. Subsequent treatment of the 4-trimethylsilyloxy phosphonates **6** with 95% acetic acid[22] removes the 4-trimethylsilyl group to generate the corresponding 4-hydroxy phosphonates **7** as a 1:1 mixture of 2*S*,4*R*- and 2*S*,2*S*-diastereoisomers in 93–95% yield. The required 2-amino-4-phosphonobutyric acid derivatives isosteric with *O*-phosphonoserine are accessible by radical deoxygenation[23] of

Table 2. Protected 4-Substituted 2-Amino-4-phosphonobutanoic Acids **6–8** Prepared

Product[a]	Yield (%)	$[\alpha]_D^{20}$ (*c*, EtOAc)	^{31}P-NMR δ	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)	FAB-MS, +ve ion[d] *m/z* (%)
6a	95	−7.7° (1.1)	25.3 (s); 25.9 (s)	0.17 (s, 9H, $SiMe_3$); 1.44 (s, 9H, *t*-C_4H_9); 1.7–2.3 (m, 2H, $CHCH_2$); 3.76, 3.78 (2d, 6H, $POCH_3$, *J* = 10.5); 3.9–4.4 (m, 2H, 2×CH); 5.1 (m, 2H, CH_2Ar); 5.44 (m, 1H, NH); 7.33 (s, $5H_{arom}$)	490[(M + 1)$^+$, 29]; 434[(M + 1 − 56)$^+$, 64]
6b	99	−4.0° (0.25)	22.7 (s); 23.2 (s)	0.17 (s, 9H, $SiMe_3$); 1.31 (t, 6H, $POCH_2CH_3$, *J* = 7.1); 1.44 (s, 9H, *t*-C_4H_9); 1.65–2.3 (m, 2H, $CHCH_2$; 3.9–4.4 (m, 6H, 2×CH + $POCH_2$); 5.1 (m, 2H, CH_2Ar); 5.5 (m, 1H, NH); 7.32 (s, $5H_{arom}$)	518[(M + 1)$^+$, 9]; 462[(M + 1 − 56)$^+$, 46]
7a	93	−2.14° (0.7)	26.5 (s)	1.45 (s, 9H, *t*-C_4H_9); 1.8–2.5 (m, 2H, $CHCH_2$; 3.57, 3.63 (2d, 6H, $POCH_3$, *J* = 10.2); 3.9–4.8 (m, 2H, 2×CH); 5.1 (s, 2H, CH_2Ar); 5.9 (M, 1H, NH); 7.34 (s, $5H_{arom}$)	418[(M + 1)$^+$, 28]; 362[(M + 1 − 56)$^+$, 44]
7b	95	2.5° (0.4)	23.8 (s); 24.0 (s)	1.33 (m, 6H, $POCH_2CH_3$); 1.45 (s, 9H, *t*-C_4H_9); 2.2 (m, 2H, $CHCH_2$); 4–4.6 (m, 6H, 2×CH + $POCH_2$); 5.1 (s, 2H, CH_2Ar); 5.83 (m, 1H, NH); 7.34 (s, $5H_{arom}$)	446[(M + 1)$^+$, 6]; 390[(M + 1 − 56)$^+$, 16]
8a	95	15.0° (0.4)	20.3 (s); 19.9 (s)	1.4, 1.45 (2s, 9H, *t*-C_4H_9); 2.51 (m, 2H, $CHCH_2$); 3.75, 3.78 (2d, 6H, $POCH_3$, *J* = 10.9); 4.31 (m, 2×CH); 5.0, 5.1 (2s, 2H, CH_2Ar); 6.1 (m, 1H, NH); 7.03 (s, $1H_{het}$); 7.3, 7.32 (2s, $5H_{arom}$); 7.63, 8.34 (2s, 2×$1H_{het}$)	472[(M + 1 − 56)$^+$, 11]; 418[(M + 1 − 110)$^+$, 30]
8b	95	−10° (0.4)	17.3 (s); 17.6 (s)	1.29 (m, 6H, $POCH_2CH_3$); 1.4, 1.45 (2s, 9H, *t*-C_4H_9); 2.6 (m, 2H, $CHCH_2$); 4–4.35 (m, 6H, 2×CH + $POCH_2$); 5.0, 5.6 (2s, 2H, CH_2Ar); 6.25 (m, 1H, NH); 7.03 (s, $1H_{het}$); 7.3 (s, $5H_{arom}$); 7.6, 8.34 (2s, 2×$1H_{ket}$)	446[(M + 1 − 110)$^+$, 15]; 312[(M + 1 − 244)$^+$, 6]

[a] All compounds in Table 2 were homogeneous by TLC (silica gel).
[b] 40.26 MHz, chemical shifts relative to 85% H_3PO_4 (external standard).
[c] 100 MHz spectra.[20]
[d] Samples prepared in a glycerol/solvent matrix and ionized by bombardment with argon ions.

Table 3. Protected 2-Amino-4-phosphonobutanoic Acids **9–11** Prepared

Product[a]	Yield (%)	$[\alpha]_D^{20}$ (*c*, EtOAc)	^{31}P-NMR ($CDCl_3$)[b], δ	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)	MS[d] *m/z* (%)
9a	98	−2.14° (0.7)	33.7 (s)	1.44 (s, 9H, *t*-C_4H_9); 1.45–2.27 (m, 4H, $CHCH_2CH_2$); 3.68 (d, 6H, $POCH_3$, *J* = 11); 4–4.36 (m, 1H, CH); 5.08 (s, 2H, CH_2Ar); 5.97 (d, 1H, NH, *J* = 8); 7.32 (s, $5H_{arom}$)	401(M^+, 1); 354[$(M-56)^+$, 8]
9b	99	−1.6° (0.75)	30.9 (s)	1.28 (t, 6H, $POCH_2CH_3$, *J* = 7.1; 1.44 (s, 9H, *t*-C_4H_9); 1.45–2.27 (m, 4H, $CHCH_2CH_2$); 3.91–4.4 (m, 5H, CH + $POCH_2$); 5.09 (s, 2H, CH_2Ar); 5.87 (d, 1H, NH, *J* = 7); 7.32 (s, $5H_{arom}$)	429[M^+, 0.5]; 373[$(M-56)^+$, 4]
10a	75	8.34° (0.6)	34.5 (s)	1.6–2.26 (m, 4H, $CHCH_2CH_2$); 3.69 (d, 6H, $POCH_3$, *J* = 10.7); 4.37 (m, 1H, CH); 5.08 (s, 2H, CH_2Ar); 5.94 (d, 1H, NH, *J* = 8); 7.31 (s, $5H_{arom}$); 10.0 (s, 1H, CO_2H)	345[M^+, 10]
10b	75	9.35° (2.1)	31.8 (s)	1.27 (t, 6H, $POCH_2CH_3$, *J* = 7); 1.6–2.6 (m, 4H, $CHCH_2CH_2$); 4.32 (m, 1H, CH); 4.6 (dq, 4H, $POCH_2$, *J* = 7.2); 5.08 (s, 2H, CH_2Ar); 5.94 (d, 1H, NH, *J* = 8); 7.32 (s, $5H_{arom}$); 10.0 (s, 1H, CO_2H)	373[M^+, 0.6]
11a[31]	94	13.3° (0.6)	34.6 (s)	1.44 (s, 9H, *t*-C_4H_9); 1.5–2.2 (m, 4H, $CHCH_2CH_2$); 3.75 (d, 6H, $POCH_3$, *J* = 10.6); 4.3 (m, 1H, CH); 5.47 (d, 1H, NH, *J* = 7); 10.1 (s, 1H, CO_2H)	312[$(M+1)^+$, 31]; 212[$(M+1-100)^+$, 100]
11b[31]	95	−25.0° (0.32)	31.8 (s)	1.32 (t, 6H, $POCH_2CH_3$, *J* = 7.1); 1.45 (s, 9H, *t*-C_4H_9); 1.62–2.34 (m, 4H, $CHCH_2CH_2$); 4.12 (dq, 4H, $POCH_2$, *J* = 7.3); 4.3 (m, 1H, CH); 5.45 (br, 1H, NH); 10.0 (s, 1H, CO_2H)	340[$(M+1)^+$, 9]; 240[$(M+1-100)^+$, 51]

[a] All compounds in Table 3 were homogeneous by TLC (silica gel).
[b] 40.2 MHz, chemical shifts relative to 85% H_3PO_4 (external standard).
[c] 100 MHz spectra.
[d] For compounds **11a** and **11b**, the molecular ions were obtained using FAB-mass spectrometry. Samples prepared in a glycerol/solvent matrix and ionized by bombardment with argon ions.

the 4-hydroxy phosphonates **7**. Deoxygenation of the 4-position of hydroxy phosphonates **7** is achieved by prior conversion to the 4-imidazolylthiocarbonyloxy derivatives.[24] Hence, reaction of **7** with 1,1-thiocarbonyldiimidazole in refluxing[25] 1,2-dichloroethane affords the *O*-imidazolylthiocarbonyl derivatives **8** as a 1:1 mixture of 2*S*,4*R*- and 2*S*,4*S*-diastereoisomers in 95% yield. Reduction of the **8** with tributyltin hydride in refluxing benzene proceeds smoothly to yield the protected phosphonates **9** in yields of 98–99% (Table 3).

The choice of benzene as reaction solvent is crucial, because the use of the higher boiling toluene, normally employed for reductions of this type, causes decomposition of **8**.

The protected phosphonates **9** may be converted to the *N*-*tert*-butyloxycarbonyl derivatives, which are used most commonly in solid phase peptide synthesis procedures as devised by Merrifield.[26] Treatment of phosphonates **9** with 4 M hydrochloric acid in dioxane selectively removed the *tert*-butyl ester group to generate the free acids **10** in 75% yield. Catalytic hydrogenolysis of the free acids **10** with palladium acetate[27] in acetic acid quantitatively removes the *N*-benzyloxycarbonyl group, and acylation of the acetate salt produced with di-*tert*-butyl dicarbonate gives the *N*-*tert*-butyloxycarbonyl protected phosphonates **11** in 94–95% yield (Scheme **B**, Table 3). The optical purity of protected phosphonates **11** was estimated at 99% using a HPLC modification of the Manning–Moore procedure.[13] Preliminary work[28] using phosphonates for peptide synthesis has shown that these derivatives couple in high yield and the alkyl protecting groups may be removed with either 45% hydrobromic acid in acetic acid[29] or 10% trimethylsilyl bromide in acetonitrile[30] without loss of optical activity.

^{1}H-, ^{13}C- and ^{31}P-NMR spectra were obtained using a JEOL-FX-100 spectrometer. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. Electron impact and chemical ionization mass spectra were recorded with a VG Micromass 7070F high resolution mass spectrometer operating with an ionizing potential of either 15 or 70 eV. Fast Atom Bombardment mass spectra were obtained using a JEOL-DX-300 mass spectrometer equipped with a FAB source. HPLC was performed on an Altex liquid chromatograph with an ultrasphere ODS reverse phase column (0.46 × 25 cm). THF was distilled from potassium benzophenone ketyl before use. Benzene was dried over 3Å molecular sieves, and CH_2Cl_2 and dioxane were dried by passage through a small column (4 × 8 cm) of neutral Al_2O_3. Thin layer chromatography was performed on silica gel plates (3 × 6 cm) with visualization by iodine vapour. Flash chromatography were performed with glass columns packed with silica gel 60 (400–230 mesh).

Aspartic acid derivative **1** was prepared in 72% overall yield from (*S*)-aspartic acid as previously described[15] and isolated as a colorless oil.

1-*tert*-Butyl Methyl (*S*)-*N*-Benzyloxycarbonylaspartate (2):
A solution of **1** (25.5 g, 90.7 mmol) in CH_2Cl_2 (200 mL) is cooled to −5°C (ice-salt bath) and H_2SO_4 (0.9 mL) added. Isobutene (12 g) is passed into the solution, and after 48 h at room temperature, excess isobutene is removed by degassing at water pump pressure. The organic layer is washed with H_2O (2 × 200 mL), 5% $NaHCO_3$ (2 × 200 mL), H_2O (100 mL), and dried (Na_2SO_4). The solvent is evaporated at reduced pressure to give **2** as an oil; yield: 26.5 g (85%).

1-*tert*-Butyl Hydrogen (*S*)-*N*-Benzyloxycarbonylaspartate (3):
Methyl ester **2** (48.0 g, 142.3 mmol) is dissolved in MeOH (100 mL) and 2 M NaOH (72 mL), and stirred at room temperature for 3 h. MeOH is removed at reduced pressure and the remaining aqueous layer washed with ether (2 × 30 mL), and the ether washes discarded. The aqueous layer is acidified to pH 2 with 3 M HCl and extracted with EtOAc (2 × 50 mL). The combined organic phase is washed with H_2O (50 mL), dried (Na_2SO_4), and the solvent is evaporated at reduced pressure to afford **3** as an oil; yield: 42.2 g (92%).

***tert*-Butyl (*S*)-*N*-Benzyloxycarbonylhomoserinate (4):**
A solution of **3** (6.55 g, 20.0 mmol) in dry THF (20 mL) is cooled to −10°C and *N*-methylmorpholine (2.03 g, 20 mmol) is added. After 1 min at −10°C, ethyl carbonochloridate (2.17 g, 20 mmol) is added dropwise and the mixture stirred at −5°C for a further 15 min. *N*-methylmorpholine hydrochloride is removed by filtration, and the filtrate is added over a period of 10 min to a vigorously stirred suspension of $NaBH_4$ (1.67 g, 45 mmol) in H_2O (10 mL) at 5–10°C. The mixture is stirred at room temperature for 3.5 h, cooled at 5°C, acidified to pH 2 with 3 M HCl and extracted with EtOAc (2 × 50 mL). The organic extract is washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and the solvent is evaporated at reduced pressure to give **4** as an oil; yield: 5.25 g (85%).

(*S*)-*N*-Benzyloxycarbonylaspartaldehyde *tert*-Butyl Ester (5):
Dry CrO_3 (15 g, 150 mmol) is added to a stirred solution of dry pyridine (27.2 mL) in dry CH_2Cl_2 (190 mL). After stirring at room temperature for 20 min, the dark red solution is cooled to 5–10 °C, and a solution of **4** (7.82 g, 25.3 mmol) in CH_2Cl_2 (20 mL) is added in one portion, and stirring continued at room temperature. After total consumption of **4** (usually 1.5 h as determined by TLC analysis), the solution is decanted from the residue and the residue washed with CH_2Cl_2 (2 × 30 mL). The solvent is removed at reduced pressure and the brown oil obtained dissolved in ether (150 mL). The organic phase is washed with 1 M HCl (2 × 200 mL), 5% $NaHCO_3$ (100 mL), H_2O (100 mL), and dried (Na_2SO_4). The solvent is evaporated at reduced pressure and the residual crude **5** purified by column chromatography on silica gel using EtOAc/pentane (2:3) as eluent; oil; yield: 4.66 g (60%).

***tert*-Butyl (2*S*,4*R*)- and (2*S*,4*S*)-2-(Benzyloxycarbonylamino)-4-dimethoxyphosphoryl-4-trimethylsilyloxybutanoate (6a); Typical Procedure:**
A solution of aldehyde **5** (3.32 g, 10.8 mmol) and dimethyl trimethylsilyl phosphite (3.0 g, 16 mmol) in dry benzene (40 mL) is refluxed for 1 h, cooled to room temperature, and H_2O (20 mL) added. The organic phase is washed with brine (20 mL), and dried (Na_2SO_4). The solvent is evaporated at reduced pressure and the residual crude **6a** purified by column chromatography on silica gel using EtOAc/pentane (3:1) as eluent; oil; yield: 5.02 g (95%).

***tert*-Butyl (2*S*,4*R*)- and (2*S*,4*S*)-2-(Benzyloxycarbonylamino)-4-dimethoxyphosphoryl-4-hydroxybutanoate (7a); Typical Procedure:**
The trimethylsilyloxy phosphonate **6a** (4.90 g, 10 mmol) is dissolved in 95% aq. AcOH (20 mL) and left at room temperature for 24 h. The solvent is removed at reduced pressure, and the residue dissolved in EtOAc (40 mL). The organic layer is washed with water (2 × 20 mL), dried (Na_2SO_4), and the solvent removed at reduced pressure to give **7a** as an oil; yield: 3.6 g (93%).

***tert*-Butyl (2*S*,4*R*)- and (2*S*,4*S*)-2-(Benzyloxycarbonylamino)-4-dimethoxyphosphoryl-4-(imidazolylthiocarbonyloxy)butanoate (8a); Typical Procedure:**
1,1′-Thiocarbonyldiimidazole (7.13 g, 40 mmol) is added to a solution of **7a** (20 mmol) in dry 1,2-dichloroethane (50 mL). The mixture is heated at 70 °C for 2–3 h, cooled to 5 °C and water (20 mL) added. The aqueous phase is washed with cold solutions of 1 M HCl (2 × 20 mL), 5% $NaHCO_3$ (20 mL), H_2O (20 mL) and dried (Na_2SO_4). The solvent is removed at reduced pressure to give **8a** as a yellow oil; yield: 8.95 g (95%).

***tert*-Butyl (*S*)-2-(Benzyloxycarbonylamino)-4-dimethoxyphosphorylbutanoate (9a); Typical Procedure:**
Tributyltin hydride (4.36 g, 15 mmol) is added to a solution of **8a** (5.3 g, 10 mmol) in dry benzene (30 mL) and the mixture refluxed for 1.5 h. The mixture is cooled to room temperature and the solvent removed at reduced pressure. The resulting oily residue is partitioned between MeCN (30 mL) and hexane (10 mL). The hexane layer is discarded and the MeCN layer washed with hexane (3 × 10 mL). After removal of the MeCN at reduced pressure, the residue is dissolved in EtOAc (30 mL) and washed with 1 M HCl (10 mL) and water (10 mL). The organic phase is dried (Na_2SO_4) and the solvent removed at reduced pressure to give **9a** as an oil; yield: 3.9 g (98%).

(*S*)-2-(Benzyloxycarbonylamino)-4-dimethoxyphosphorylbutanoate (10a); Typical Procedure:
The *tert*-butyl ester **9a** (10 mmol) is dissolved in 4 M HCl/dioxane (10 mL) and left at room temperature for 6 h. The solvent is removed at reduced pressure and the residue dissolved in EtOAc (25 mL). The organic phase is extracted with 5% $NaHCO_3$ (3 × 20 mL) and the combined base extracts acidified to pH 2 with 1 M HCl. The aqueous phase is extracted with EtOAc (3 × 10 mL) and the combined organic layer washed with water (2 × 5 mL) and dried (Na_2SO_4). The solvent is removed at reduced pressure to give **10a** as an oil; yield: 2.58 g (75%).

(*S*)-2-(*tert*-Butyloxycarbonylamino)-4-dimethoxyphosphorylbutanoate (11a); Typical Procedure:
$Pd(OAc)_2$ (0.15 g) is added to a solution of **10a** (2.0 g, 5.8 mmol) in glacial AcOH (20 mL). The mixture is hydrogenolyzed at atmospheric pressure until hydrogen uptake ceases (6–8 h). The Pd catalyst is removed by filtration and the solvent removed at reduced pressure. The residue is dissolved in H_2O (5 mL) and dioxane (5 mL) and Na_2CO_3 (0.64 g, 6 mmol) added. The mixture is cooled to 0 °C and di-*tert*-butyl dicarbonate (3.27 g, 15 mmol) added. The mixture is stirred at room temperature for 2 h and the dioxane removed at reduced pressure. The aqueous layer is washed with ether (2 × 20 mL) and the ether layers discarded. The aqueous layer is acidified to pH 2 with 1 M HCl and extracted with $CHCl_3$ (3 × 20 mL). The combined organic phase is washed with water (10 mL), dried (Na_2SO_4), and the solvent removed at reduced pressure to yield **11a** as an oil; yield: 1.7 g (94%).

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- Baldo, M.A., Chessa, G., Marangoni, G., Pitteri, B. *Synthesis* **1987**, 720. On p. 722, line 6, "degree of functionalization" should read "yield of binding". On the same page in the preparation of bis-hydrazone **5**, line 8, "solid product" should read "oil".

- Singh, L.W., Ila, H., Junjappa, H. *Synthesis* **1988**, 89. On p. 90 in the ^{1}H-NMR data for dioxime **4**, line 2, "N_2" should read "NH_2".

- Burger, K., Hübl, D., Geith, K. *Synthesis* **1988**, 194. On p. 196 in the table, for entries **4l**, **4m**, and **4n**, Y = O, and *Nu* = Cl, Br, and C_6H_5, respectively.

- Tolstikov, A.G., Khakhalina, N.V., Spirikhin, L.V. *Synthesis* **1988**, 221. In the title and abstract, benzyl esters should read benzyl ethers.

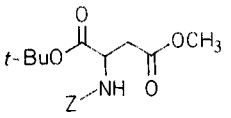
- Gupta, A.K., Ila, H., Junjappa, H. *Synthesis* **1988**, 284. Compounds **4** are 1,6-dioxo-1,2,3,6-tetrahydropyrano[3,4-*c*]pyrroles; compounds **9** are 1,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridines.

- Keshavarz-K., M., Cox, S.D., Angus, R.O., Jr., Wudl, F. *Synthesis* **1988**, 641. On p. 642 the IR spectra shown in Figures 2 and 3 should be interchanged.

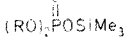
- Rodriguez, J., Waegell, B. *Synthesis* **1988**, 534. On p. 535, the first line of the general procedure should read: "DMAP (0.92 g, 7.5 mmol) and then α,β-unsaturated aldehyde **1** (0.1 mol)..."

- Zbiral, E., Drescher, M. *Synthesis* **1988**, 735. On p. 738 in the last procedure, the name for compounds **14** should read: (5-Oxo-5,6-dihydroimidazo[1,2-*c*]pyrimidin-3-yl)methylphosphonsäuren.

- Valerio, R.M., Alewood, P.F., Johns, R.B. *Synthesis* **1988**, 786. On p. 787 formula **2** should be:



Also on p. 787 in the reaction of **5** in the scheme on the right side, the reagent should be:



- Garrigues, B., Mulliez, M. *Synthesis* **1988**, 810. The title should read: Salts of *N*-(Sulfoalkyl)ureas and -thioureas.

- Yokoyama, M., Watanabe, S., Seki, T. *Synthesis* **1988**, 879. On p. 880 the name of compound **3a** in the first procedure should be azido(2-benzyloxyethoxy)methane.