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A Short Synthesis of (S)-3-(Dimethylphosphono)-2-((9-fluorenyl)methoxycarbamoyl)propionic Acid, a Protected Phosphonic Acid Analogue of Aspartic Acid

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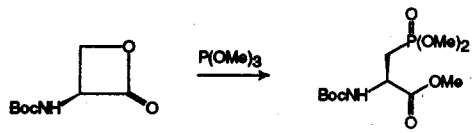
Abstract: *The synthesis, from serine, of a phosphonic acid analogue of aspartic acid protected in a form suitable for peptide synthesis, is described.*

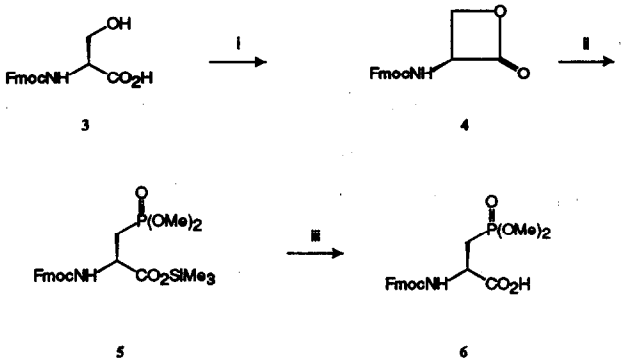
We are interested in exploring the role of aspartic acid isosteres in biologically active peptides. In particular we are studying the effect of substituting the ß-carboxylic acid group (pKa 4-5) with more strongly acidic moieties. One such entity is the phosphonic acid group (pKa 1-2). A review of the literature revealed no syntheses of 2-amino-3-phosphonopropionic acid protected in a form suitable for peptide synthesis although several syntheses of the free amino acid have been described.[1,2] The more direct of these syntheses[2], which is due to Smith and co-workers at Lilly, employs the reaction of a serine derived ß-lactone 1 with trimethylphosphite to give trimethyl ester 2. Short and attractive though this synthesis is, we could not envisage a strategy which would allow us to hydrolyse the carboxylic methyl ester in the presence of the phosphonic acid methyl esters to give a building block for peptide synthesis.



1 2

Scheme 1

However, we were aware that not only are silylphosphites more nucleophilic than alkyl phosphites, but that trimethylsilyl groups are lost in preference to alkyl groups in the Arbusov reaction.[3] We therefore speculated that the reaction of dimethyl(trimethylsilyl)phosphite with lactone 4 would lead specifically to the carboxylic trimethylsilyl ester by preferential transfer of the trimethylsilyl group. A simple aqueous work up should then hydrolyse the silyl ester 5 to give the N- and P-protected free carboxylic acid 6 ready for activation and coupling. These expectations were gratifyingly borne out in practice (Scheme 2). The deprotection of phosphonic acid methyl esters with trimethylsilylbromide or 45% hydrogen bromide in acetic acid in peptides containing (S)-2-amino-4-(dimethylphosphono)butyric acid, the phosphonic analogue of glutamic acid, has been reported, and it is expected that these intermediates will react similarly.[4]



Reagents: i) PPh_3, Dimethyl azodicarboxylate ii) $(Me_3SiO)P(OMe)_2$ iii) H_2O

Scheme 2

Thus a suspension of (S)-3-((9-fluorenyl)methoxycarbamoyl)oxetan-2-one 4 (3.36g), prepared in 73% yield from N-((9-fluorenyl)methoxycarbonyl)-L-serine analogously to the method of Arnold *et al.*,[5] in dimethyl(trimethylsilyl)phosphite[6] (20ml), was heated under argon with stirring at 100°C until the reaction mixture was homogeneous (25h). The excess phosphite was evaporated under reduced pressure and the residue taken up in ethyl acetate (600ml) and washed with water (4 x 200ml), dried ($MgSO_4$) and re-evaporated. The resulting gum was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:acetic acid (400:16:3), to give 2.60g (57%) of a colourless foam which was recrystallised from acetonitrile to give 1.75g (39%) of analytically[7] and optically[8] pure (S)-3-(dimethylphosphono)-2-((9-fluorenyl)methoxycarbamoyl)propionic acid.

Acknowledgements

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References

1. Villanueva, J. M.; Collignon, N.; Guy, A.; Savignac, P. *Tetrahedron*, 1983, *39*, 1299.
2. Smith, E. C. R.; McQuaid, L. A.; Paschal, J. W.; De Honiesto, J. *J. Org. Chem.*, 1990, *55*, 4472.
3. Wozniak, L.; Chojnowski, J. *Tetrahedron*, 1989, *45*, 2465.
4. Valerio, R.M.; Alewood, P.F.; Johns, R.B. *Synthesis*, 1988, 786.
5. Arnold, L. D.; T H Kalantar, T. H.; Vederas, J.C. *J. Amer. Chem. Soc.*, 1985, *107*, 7105.
6. Sekine, M.; Futatsugi, T.; Yamada, K.; T Hata, T. *J. Chem. Soc. Perkin Trans 1*, 1982, 2509.
7. M.Pt. 134°C. C 57.32, H 5.20, N 3.44 (Calculated for $C_{20}H_{22}O_7NP$ C 57.28, H 5.29, N 3.34). m/z (FAB) 420(15, M^++1), 198(41), 179(100), 178(98), 165(20), 152(48), 120(10), 109(18). ^{1}H(400MHz) δ($CDCl_3$) 2.55(2H, dd J=6,17Hz, CH_2P), 3.72(3H, d J=11Hz, POMe), 3.79(3H, d J=11Hz, POMe), 4.23(1H, t J=6Hz, Fmoc), 4.40(2H, m Fmoc), 4.55-4.68(1H, m, NCH), 6.17(1H, d J=6Hz, NH), 7.25-7.45, 7.56-7.65 and 7.75(8H, m, Fmoc). ^{31}P (162MHz) δ($CDCl_3$) 28.38.
8 $[\alpha]^{20}_D$ -13.1°(1% MeOH). Attempts to detect the presence of any enantiomer by chiral hplc on a variety of supports or by ^{1}H or ^{31}P nmr in the presence of Pirkle's Reagent were unsuccessful.

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