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A practical method for the combinatorial synthesis of peptide aldehydes

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Abstract: A practical strategy for solid phase synthesis of peptide aldehydes is described. An olefin linker is constructed using Wittig chemistry, after peptide synthesis ozonolytic treatment of the linker and subsequent workup with dimethyl sulphide results in facile isolation of peptide aldehydes. The principle is demonstrated by synthesis of a 3x3x3 array of 27 tripeptide aldehydes.

Peptide aldehydes have been found to inhibit several classes of proteolytic enzymes, with targets including HIV protease[1], human rhinovirus 3C protease[2] and interleukin-1β-converting enzyme (ICE)[3]. A simple solid phase synthesis of peptide aldehydes would facilitate a combinatorial approach to further investigation of these compounds. Martinez *et al.* have recently reported two methods for solid phase synthesis of peptide aldehydes, using Weinreb amide[4] and olefinic[5] linkers. The latter is cleaved by ozone and subsequent reaction with thiourea. In both approaches an aqueous workup is required to isolate the peptide aldehyde, leading to complications when applied to library synthesis. Schuerch and Frechet first reported the use of an olefin linker in the solid phase synthesis of glycosides of hydroxyethanal[6]. This synthesis requires a lengthy reaction sequence in order to construct the olefin linker.

As part of our investigations into the use of oxidative cleavage methods in solid phase synthesis we observed that ozonolysis of an olefin linker followed by workup with dimethyl sulphide provided a rapid and high yielding method for isolation of aldehydes and ketones. The by-products and excess reagents are easily removed under vacuum, and this method may be readily applied to library synthesis. We therefore sought to develop an improved method for construction of the required linker.

N-Protected α-amino aldehydes have been shown to participate in Wittig reactions in good yield without racemisation[7-9], and it was anticipated that this chemistry could be applied to solid phase synthesis. Amino aldehydes are prepared by reduction of the corresponding Weinreb amides (Scheme 1).

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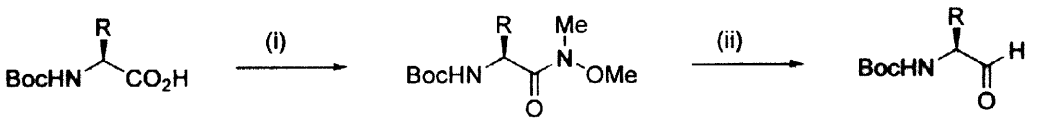
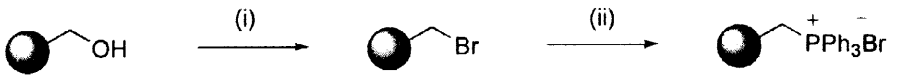


(i) MeNH(OMe).HCl / PyBOP / DIPEA / DCM / rt / 1 h
(ii) $LiAlH_4$ / Et_2O / 0°C to rt / 30 min

Scheme 1

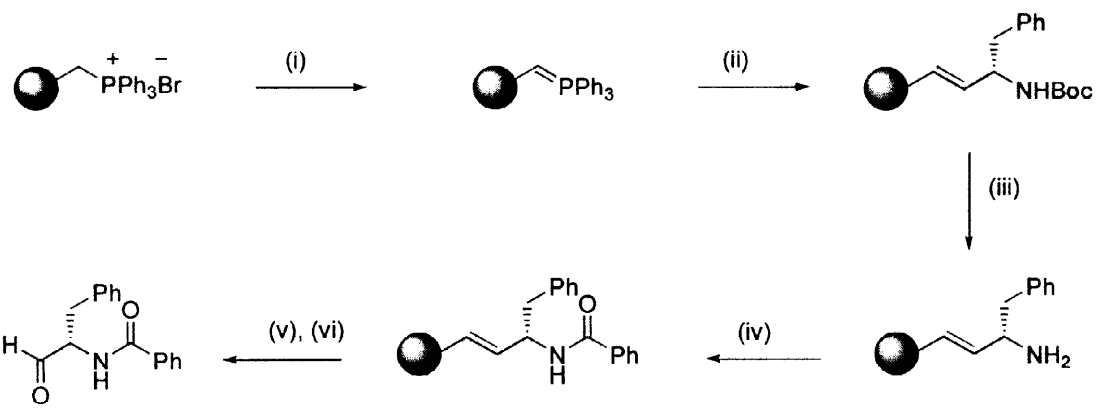
Polymer supported triphenylphosphonium bromide is prepared from hydroxymethyl polystyrene as illustrated in Scheme 2.



(i) CBr_4 / PPh_3 / CH_2Cl_2 / rt / 16 h; (ii) PPh_3 / $PhCH_3$ / Δ / 16 h

Scheme 2

In order to investigate the proposed chemistry we prepared *N*-Boc-L-phenylalaninal, and attached this to resin using Wittig chemistry. The amine was deprotected and then coupled to benzoic acid. Ozonolysis and reductive workup afforded *N*-benzoyl-L-phenylalaninal in 45% yield, characterised by LCMS and ^{1}H NMR spectroscopy (500 MHz)[10].

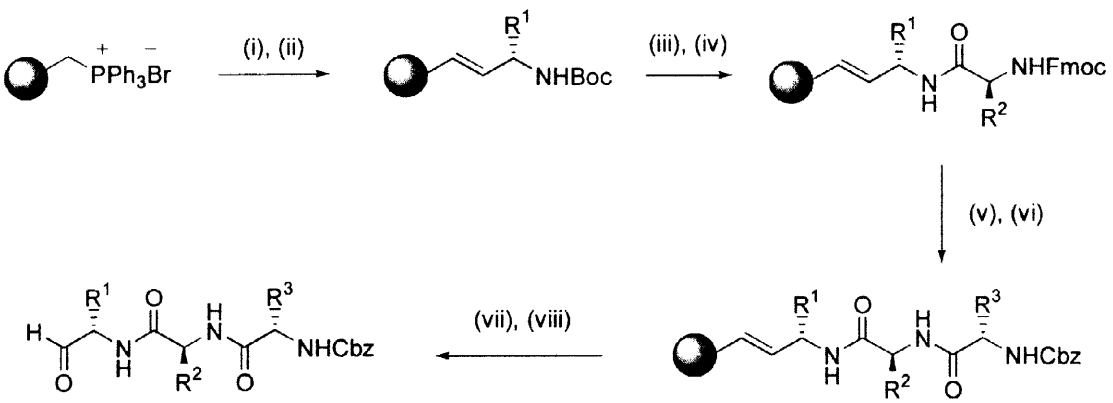


(i) NaHMDS / THF / rt / 15 min; (ii) *N*-Boc-L-phenylalaninal / THF / rt / 20 h;
(iii) 25% TFA / CH_2Cl_2 / rt / 20 min; (iv) $PhCO_2H$ / DIC / DMF / rt / 2 h;
(v) O_3 / CH_2Cl_2 / -78°C / 5 min; (vi) Me_2S / CH_2Cl_2 / 3 h

Scheme 3

We then successfully applied this strategy to the preparation of 27 tripeptide aldehydes in a 3x3x3 array. The amino acids used are shown in Table 1. Methionine was chosen as one of the *C*-terminal residues in order to study the effect of ozone on this side chain. It has been suggested[2] that a sulphone in the *C*-terminal position of a tripeptide aldehyde may mimic the binding effect of a glutamine residue and we anticipated that during ozonolysis the sulphide would be oxidised to a sulphone, thereby providing a direct route to these compounds. For each methionine-containing tripeptide aldehyde two products were observed – the corresponding sulphoxide and sulphone in approximately 50:50 ratio.

The synthesis was performed using standard peptide coupling chemistry (Scheme 4). Three amino aldehydes were prepared and reacted with three portions of polymer-supported phosphonium ylid. After TFA deprotection each resin portion was then split into three and coupled to three different *N*-Fmoc amino acids. The polymer-supported dipeptides were deprotected and each split into a further three portions before a final coupling to three different *N*-Cbz amino acids. Ozonolysis and reductive workup afforded the tripeptide aldehydes as single diastereomers after evaporation of all excess reagent and by-products. All products were characterised by LCMS and shown to be of purity > 90%.



(i) NaHMDS / THF / rt / 15 min; (ii) *N*-Boc-L-α-amino aldehyde / THF / rt / 20 h;
(iii) 25% TFA / CH_2Cl_2 / rt / 20 min; (iv) *N*-Fmoc-L-amino acid / PyBop / DIPEA / DMF / rt / 2 h;
(v) 20% piperidine / DMF / rt / 15 min; (vi) *N*-Cbz-L-amino acid / PyBop / DIPEA / DMF / rt / 2 h;
(v) O_3 / CH_2Cl_2 / -78°C / 5 min; (vi) Me_2S / CH_2Cl_2 / 3 h

Scheme 4

	Portion 1	***Portion 2***	***Portion 3***
Residue 1	Boc-Phe-H	Boc-Met-H	Boc-Val-H
Residue 2	Fmoc-Phe-OH	Fmoc-Pro-OH	Fmoc-Leu-OH
Residue 3	Cbz-Phe-OH	Cbz-Ala-OH	Cbz-Val-OH

Table 1

In conclusion we have developed an improved method for the solid phase synthesis of peptide aldehydes. The method requires only two steps in solution phase prior to attachment of the first residue to the resin. The simple cleavage procedure may be readily applied to library synthesis and gives products of high purity with no observed racemisation This has been demonstrated by the preparation of a 3x3x3 array of *N*-Cbz-protected tripeptide aldehydes.

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10. δ_H (500 MHz, $CDCl_3$) 3.32 (2H, ABX, J_{AB} 14, J_{AX}, J_{BX} 6, CH_2), 4.23 (1H, dd, *J, J'* 6, CH), 4.95 (1H, q, *J* 6, NH) 7.20-7.27 (10H, m, 2 x Ph), 9.75 (1H, s, CHO).