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CONCISE ARTICLE

Solution-phase synthesis of chiral *O*-acyl isodipeptides†

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O-Acylation of *N*-Boc-protected-serine and -threonine with *N*-Pg-(α-aminoacyl)benzotriazoles afforded the chiral *O*-acylated isodipeptides at 23 °C in yields of 74–91%.

The synthesis of peptides and proteins is of great importance to the understanding of biological functions. The solid-phase synthesis of peptides with "difficult sequences" remains problematic due to low yields and purity.[1] In addition, intermolecular hydrophobic interactions in "difficult sequences" can promote aggregation in solution and hydrogen bond networks in resin-bound peptides can form extended structures such as β-sheets.[1b–c,2]

Kiso *et al.*[1d] demonstrated that the introduction of an *O*-acyl in place of an *N*-acyl residue within a peptide backbone significantly altered the secondary structure of native peptides. Furthermore, these "*O*-acyl isopeptides" or "click peptides"‡ are more hydrophilic, and easier to purify by HPLC.[1d] He found that a subsequent *O–N* intramolecular acyl migration, triggered by change in pH, could rapidly generate a target natural peptide under physiological conditions (pH 7.4) (Fig. 1).[1c,3a] This "*O*-acyl isopeptide method"[3] has been used to develop new water-soluble taxoid prodrugs,[4] HIV-1 protease inhibitors,[5] the anti-tumor agent, paclitaxel,[6] difficult sequence-containing peptides including Ac-Val-Val-Ser-Val-Val-NH_2,[1b,4,7] Alzeheimer's disease-related amyloid *β* peptide (Aβ) 1–42,[4,7–13] and cyclic peptides.[14]

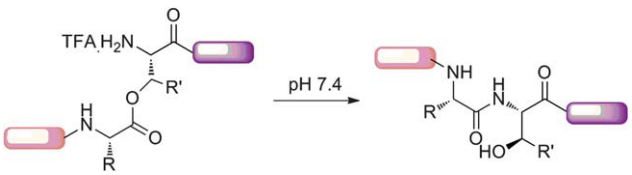
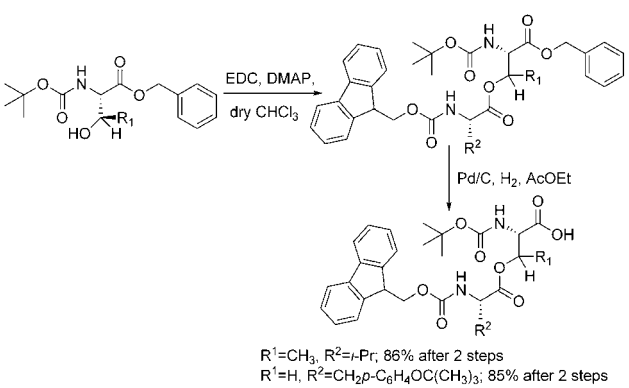


Fig. 1 *O*-Acyl isopeptide methodology.

However, epimerization during the esterification step in the solid-phase synthesis of *O*-acyl isopeptides has remained a major problem.[1c,e,15] Based on the hypothesis that epimerization during esterification should be suppressed in solution due to the faster coupling rate as compared to that on a solid support, Kiso[1c,e] synthesized *O*-acyl isodipeptides in three steps (Scheme 1): (i) protection of the carboxylic acid group in serine or threonine by benzyl esterification, (ii) *O*-acylation and (iii) deprotection using Pd/C. Treatment of Cbz-protected isodipeptides containing Cys and Met with Pd/C–H_2 failed, although catalytic hydrogen transfer (CTH) to Cys- and Met-containing protected isodipeptides gave 45% of the desired product.[1c]

We now report an efficient single-step preparation of chiral *O*-acyl isodipeptides from serine and threonine. The use of *N*-acylbenzotriazoles are advantageous for *N*-, *O*-, *C*-, *S*- acylation,[16–18] especially where the corresponding acid chlorides are unstable or difficult to prepare. *N*-(Protected-α-aminoacyl)benzotriazoles have enabled fast preparations of biologically relevant peptides and peptide conjugates in high yields and purity, under mild reaction conditions, with full retention of the original chirality.[18]

O-Acyl isoserinedipeptides **3a–h** were prepared by *O*-acylation of Boc-protected serine **1a** with various *N*-Pg-(α-aminoacyl) benzotriazoles **2** in the presence of diisopropylethylamine in CH_3CN at 23 °C for 12 h in yields of 74–90%. This proved to be the optimum condition under which neither epimerization of **3**



Scheme 1 Synthetic scheme of "*O*-acyl isodipeptide unit".

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† Electronic Supplementary Information (ESI) available: ^1H and ^{13}C NMR for compounds **2a–g**, **3a–h**, **4a–h**. See DOI: 10.1039/c1md00130b/

‡ Kiso denotes *O*-acyl peptides as "click peptides" because of their easy conversion to target native peptides under physiological conditions.[1d]