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Efficient enantioselective synthesis of orthogonally protected (*R*)-α-alkylserines compatible with the solid phase peptide synthesis

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Abstract—The Schöllkopf methodology for the asymmetric synthesis of α-amino acids, which was previously not applicable to the construction of quaternary α-amino acids, has been rendered not only suitable but also practical for this purpose and applied to a highly efficient enantioselective synthesis of orthogonally protected (*R*)-α-alkylserines suitable for the solid phase synthesis.

The enantioselective synthesis of α,α-disubstituted (quaternary) α-amino acids has recently received considerable attention since their incorporation in modified peptides often improves both the biological activity and the pharmacological profile of the latter, due to the introduction of unusual conformational constraints which change their secondary or tertiary structure.[1] Furthermore, these peptides are rendered more stable metabolically due to the decreased rate of proteolysis,[2] and sometimes quaternary α-amino acids represent powerful enzyme inhibitors.[3] Specifically, chiral nonracemic, suitably protected α-alkylserines such as **4** and **5** (Fig. 1) have been recognized as important components in the areas of both synthetic and medicinal chemistry.[4]

This recognition is attributed to the fact that their hydroxyl groups stabilize the secondary structure of peptides by hydrogen bonding with the amide carbonyl groups, thus rendering α-alkyl serines useful in peptidomimetic drug design.[5] In addition, the α-substituted serine unit is contained within several natural products such as salinosporamide A, myriocin, (+)-lactacystin, (+)-conangenin, sphingofungin E, altemicidin, and amicetin.[6]

Figure 1. The structures of orthogonally protected (*R*)-α-alkylserines.

Reported methods for the synthesis of α-substituted serines include rearrangement of chiral (nonracemic) trichloroacetimidates,[6b,7] ring-opening of chiral aziridines,[8] enzymatic desymmetrization,[6d,9] an intramolecular version of the asymmetric Strecker reaction,[10] phase-transfer catalytic enantioselective alkylation,[11] and alkylation of chiral amino acid enolate equivalents.[4d,12] One of the most notable examples of the latter approach is the bis-lactim ether methodology developed by Schöllkopf.[13] We have recently reported an improved Schöllkopf protocol for the construction of quaternary α-amino acids and applied it to efficient syntheses of β-lactams and integrin LFA-1 antagonist BIRT-377.[14] Despite its broad utility in both synthetic and medicinal chemistry,[4,5] to the best of our knowledge only one method has been reported for the synthesis of (*S*)-N^{α}-Fmoc-α-methylserine which was not orthogonally protected (free hydroxyl and carboxyl groups).[15]

In this letter, we report an efficient enantioselective synthesis of orthogonally N^{α}-Fmoc protected (*R*)-α-alkylserines employing the highly improved Schöllkopf protocol we have developed (Fig. 1).[14] Accordingly, readily available (*S*)-bislactim ether **1**[16] was deprotonated with *tert*-BuLi (−78°C, THF, 1 h) instead of *n*-BuLi used by Schöllkopf and co-workers,[12c,13] and

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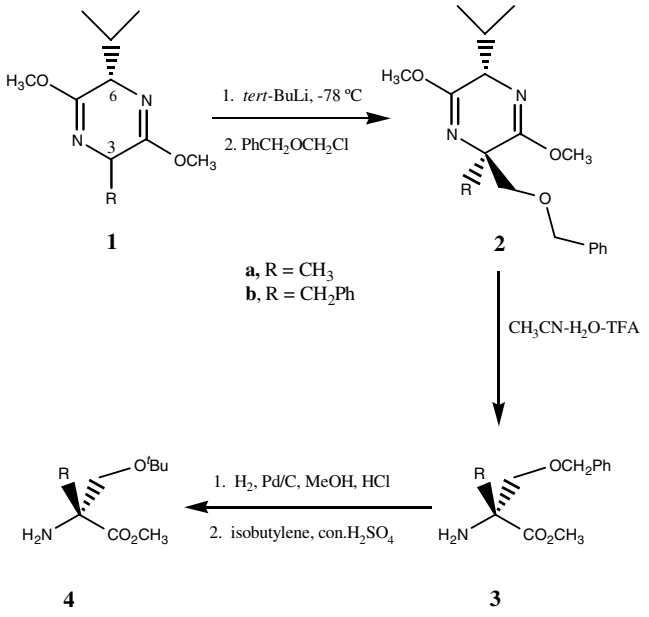
alkylated with chloromethyl benzyl ether[17] to produce (3*R*)-**2** in excellent yields (**2a**:[12c] 86%, **2b**: 90%) and very high diastereoselectivity (>95%, only one diastereomer could be detected by ^{1}H and ^{13}C NMR). Notably, the yield of **2a** using *n*-BuLi as the deprotonating base was only 58% as opposed to 91% reported by Schöllkopf and co-workers.[12c] Consistently, the yield of **2b** using *n*-BuLi was very low (35%).[18] These significant yield disparities are attributed to the exclusively basic action of *tert*-BuLi toward the less hindered C-3 hydrogen as opposed to the C-6 one, as well as its negligible nucleophilicity toward the imino esters (Scheme 1).[14]

The acidic hydrolysis of **2** with 10% trifluoroacetic acid in acetonitrile/water (2/1) for 10 h at ambient temperature[13c] afforded **3** in good yields (**3a**: 80%, **3b**: 85%). Reductive cleavage of the benzyl group on palladium in methanol/3% HCl (5/1) proceeded smoothly to provide the corresponding methyl ester hydrochloride salts, whose hydroxyl side chain was protected as *tert*-butyl ethers **4** in very good yields (**4a**: 70%, **4b**: 80%, Scheme 1, Fig. 1).[19]

Hydrolysis of **4** with aqueous NaOH (0.25 N, 0 °C, 2 h) generated the free α-amino acids which were protected as their Fmoc derivatives **5** (Fig. 2), after neutralization (2 N HCl) and addition of Fmoc–Cl in 10% aq Na_2CO_3 and dioxane, in good yields (**5a**: 55%, **5b**: 65%; two steps) and very high ee (≫95%).[20]



Scheme 1. Schöllkopf-type enantioselective synthesis of orthogonally protected (*R*)-α-alkylserines.

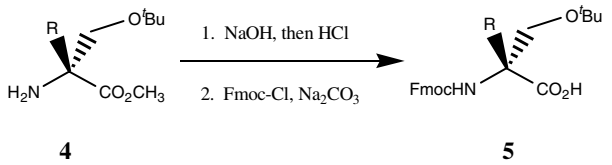


Figure 2. The conversion of orthogonally protected (*R*)-α-alkylserine **4** to **5**.

In summary, we have shown that the Schöllkopf methodology can be conveniently employed for the enantioselective construction of quaternary α-amino acids in a practical manner,[4,13] and we have applied this protocol to the synthesis of α-alkyl α-amino ester **3** (Scheme 1),[21] which has been efficiently converted to orthogonally protected (*R*)-α-alkylserines **4** and **5**, useful for the solid phase peptide synthesis. The advertized efficiency of this method relies on both the ready availability of **1**,[16] and the two-step, one-pot conversions of **3** to **4** and **4** to **5** in very good overall yields.

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Supplementary data

The experimental procedures and spectral data for products **2**–**5** as well as HPLC data on the optical purity of **5a** and **5b**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.016.

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