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Synthesis of an Orthogonally-Protected Bifunctional Amino Acid for Conformationally Constrained Peptides

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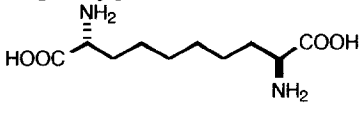
Abstract: The asymmetric synthesis of (*2S, 9R*)-2,9-diaminodecanedioic acid, orthogonally protected for incorporation into cyclic peptides by solid-phase synthesis, is described.

Peptide secondary structure mimetics can be synthesised by linking two amino acid side-chains to form a conformationally restrained cyclic peptide.[1] Recent work on the design of stable α-helical peptide mimetics, constrained in this manner, has focused on forming amide bonds between Glu/Asp and Lys residues at positions i and i+4 of the helix,[2] on incorporating artificial metal binding residues,[3] on forming salt bridges between these positions,[4] and on linking positions i and i+7 by forming disulfide bonds between two cysteine homologue residues.[5] The potential drawbacks of linking the hydrophilic residues in a biologically active helical peptide,[6] and the benefits for drug design of incorporating unnatural amino acids into peptide secondary structure mimetics,[7] led us to consider attempting to stabilise a helical conformation by placing an aliphatic linkage between the i and i+4 positions.

Our preliminary modelling studies indicated that (*2S, 9R*)-2,9-diaminodecanedioic acid **1** could be incorporated into peptides to stabilise a helical conformation in this way. A solid-phase approach to the synthesis of such a cyclic peptide, using the methodology recently described by Albericio,[8] would involve the use of the orthogonally protected amino acid **2**.



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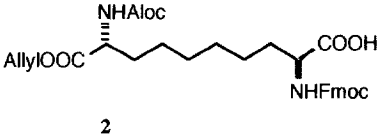
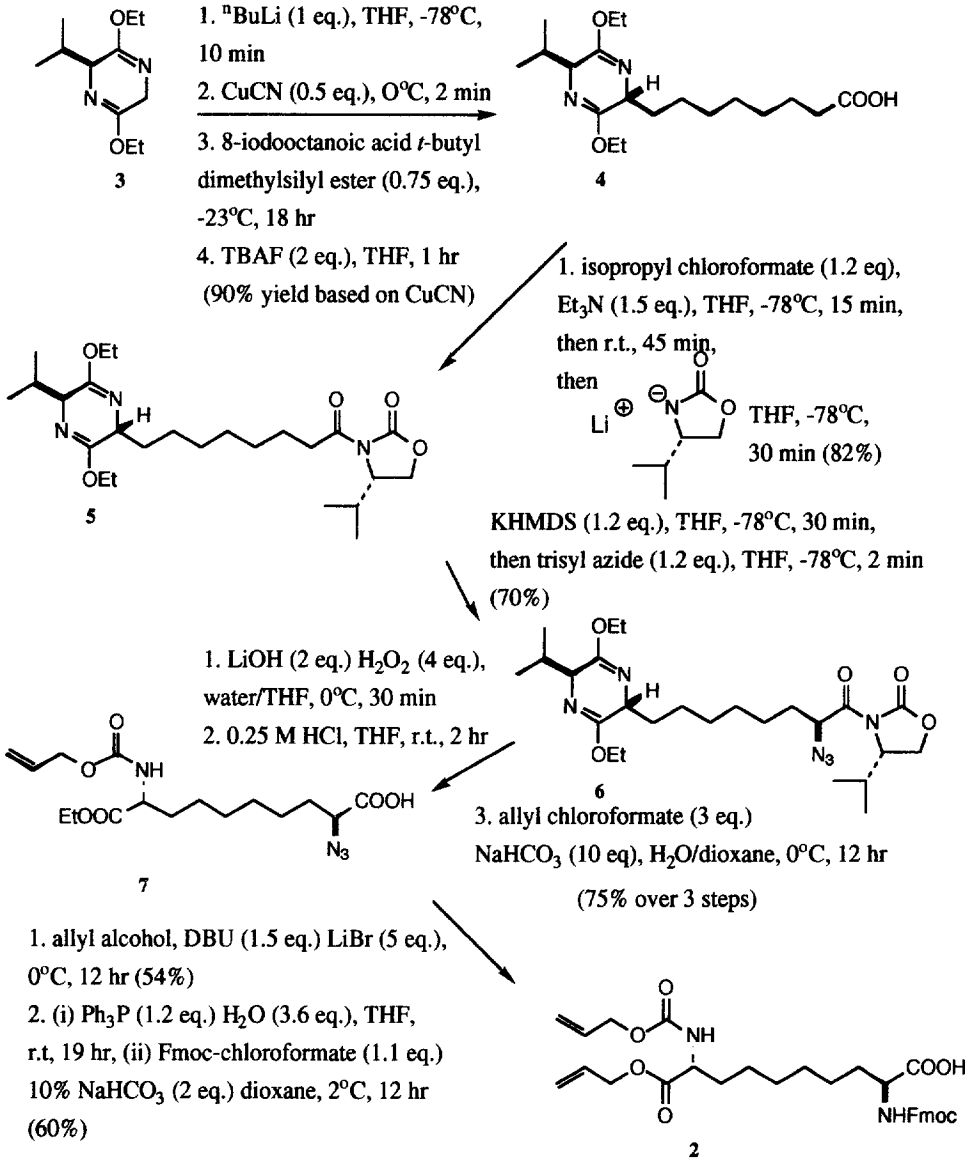


2

The synthesis of this differentially protected bifunctional amino acid presents certain challenges. Two amino acid groups of opposing chirality must be installed; as the chiral centres are remote from each other, this necessitates the use of two separate enantiospecific methodologies. The method should then allow each functional group to be selectively treated in such a way that like groups can be differentiated.[9] Here we report a short, enantioselective synthesis of **2**, which fulfils these criteria.

The synthetic sequence is shown in Scheme 1. We envisaged using the Schöllkopf method[10] to install the (*R*)-stereocentre; however, our initial efforts to generate this chiral centre using the lithium azaenolate of the bislactim ether **3**, and various esters of 8-iodooctanoic acid, gave only low yields with high recovery of starting bislactim ether. We believe this is due to the high basicity of the lithium azaenolate. We therefore used the recently described higher order bislactim ether lithium cyanocuprate,[11] which has been shown to give good results with more complex substrates. 8-Iodooctanoic acid *t*-butyldimethylsilyl ester was used as the

electrophile. This was conveniently prepared in two steps from 8-bromooctanoic acid, which was converted to the iodo acid using sodium iodide in acetone and then protected as the *t*-butyldimethylsilyl ester. Coupling of this material to the bislactim ether lithium cyanocuprate, followed by immediate removal of the *t*-butyldimethylsilyl group by reaction with TBAF, gave the desired **4** in 90% yield.[12]



Scheme 1

To introduce the (*S*)-stereocentre, **4** was first coupled to the Evans auxiliary to give the N-acyl oxazolidone **5**. Enolisation with KHMDS, followed by reaction with 2,4,6-triisopropylbenzenesulphonyl azide (trisyl azide),[13] served to introduce the azido group, via a hydrazide adduct. The standard workup conditions[13] for this reaction resulted in the hydrolysis of the acid-labile bis-lactim ether, forming the amino acid ethyl ester at the (*R*)-stereocentre. As revealing this chiral centre at this stage would have made subsequent differentiation of the two carboxylic acids difficult, a modified protocol was used[14] giving **6** in 82% yield.[15]

The chiral centres were then sequentially unmasked, giving the product in a form that allowed differentiation of the chiral centres by selective protection. Cleavage of the oxazolidone using lithium hydroperoxide[13] to give the (*S*)-chiral free acid was immediately followed by hydrolysis of the bislactim with aqueous acid.[9] The resulting amino diacid monoester was immediately protected with allyl chloroformate[16] to give **7**. In order to carry out a selective transesterification to give the allyl ester, a base-catalysed method was required, as it was unlikely that the free carboxylic acid would also react in a basic medium. The method described by Seebach[17] (0.5 eq. DBU, 5 eq. LiBr) was selected, as it was reported to give high yields with little or no racemisation. Using these conditions, the desired allyl monoester was produced selectively in high yield, with no trace of diester formation nor of epimerisation. The azido group was then reduced to the amine using triphenylphosphine/water[16] and protected using Fmoc-chloroformate[18] to give **2**.

In summary, a short, enantioselective synthesis of **2** has been described, with the amino and carboxylic acid groups selectively and unambiguously protected. This method should be applicable to the synthesis of other differentially protected bifunctional amino acids. The incorporation of **2** into cyclic peptides is presently in progress.

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12. Satisfactory analytical and spectral data were obtained for all compounds.
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15. The chiral purity of the stereocentres was checked at all stages by 400 MHz nmr. In addition, the chiral purity of the key intermediates **4** and **5**, and of the amino acid **2** were checked using hplc (CHIRALCEL OD® chiral hplc column (Daicel Chemical Industries, Ltd.), 250 x 4.6 mm). The retention time of **4** (isocratic, 2% ^{i}PrOH/hexane) was 3.94 min, the retention time of **5** (isocratic, 2% ^{i}PrOH/hexane) was 13.58 min, and the retention time of **2** (isocratic, 10% ^{i}PrOH/hexane) was 11.9 min. In all cases, the unwanted diastereoisomers were not detected, either by nmr or by hplc. The optical rotations of these compounds were as follows: **4**, $[\alpha]_D^{\circ}$ = -24.7° ($CHCl_3$, c=2.83 mg/ml); **5**, $[\alpha]_D^{\circ}$ = +35.3° ($CHCl_3$, c=2.72 mg/ml); **2**, $[\alpha]_D^{\circ}$ = -6.80° ($CHCl_3$, c=3.1 mg/ml)
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