

Synthesis of linear D-*alt*-L peptidomimetics starting from a carbohydrate precursor

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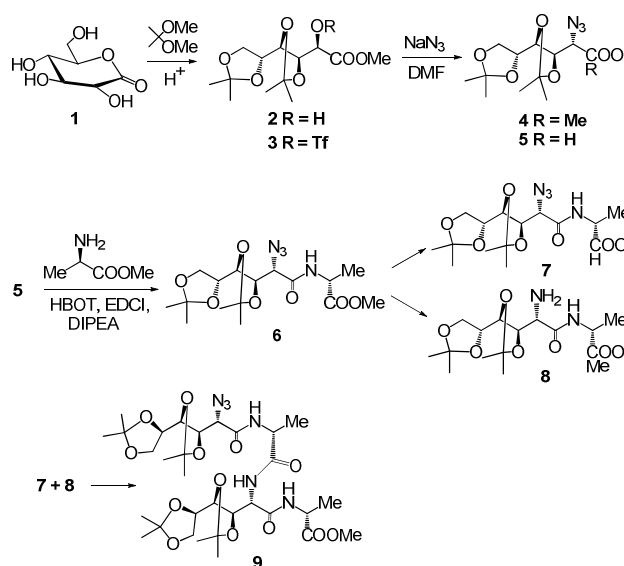
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INTRODUCTION

Fundamental building blocks used by nature are amalgamated to produce natural-like, yet unnatural, structural entities with multifunctional groups anchored in a single ensemble. For example, hybrid molecules that maintain the basic structure of a carbohydrate have been obtained. These hybrids include amino and carboxyl functional groups, characteristic of amino acids. Diverse arrays of peptidic templates have been employed for the construction of homo- and heterooligomers that behave as peptidomimetics. These molecules are sometimes able to associate themselves spontaneously (self-assembly process) to form complex architectures.¹ The novel materials find useful applications as microelectronics, drug delivery and tissue engineering. The linear oligopeptides are also precursor of cyclic peptoids (carbopeptoids) useful as molecular receptors.² We describe herein the synthesis of an amino acid building block starting from inexpensive D-Glucono-1,5-lactone. As the amino containing stereocenter possesses the *S* configuration, the molecule is combined with D-alanine (*R* configuration) to give D-*alt*-L peptides to favor self-assembly processes.

RESULTS AND DISCUSSION

Treatment of D-Glucono-1,5-lactone (**1**) with 2,2-dimethoxypropane led to conversion into the methyl ester and simultaneous protection as the 3,4:5,6-di-O-isopropylidene derivative (**2**). The free hydroxyl group was substituted by azide to obtain **4**, via the triflate **3**. Treatment of **4** with bis(tributyltin) oxide [(Bu₃Sn)₂O] gave the free carboxylic acid **5**, without racemization or elimination at C-2, as happened with other bases. Coupling of **5** with D-alanine in the presence of 1-hydroxybenzotriazole (HOBt), *N,N*-diisopropylethylamine (DIPEA) and a carbodiimide (EDCI) afforded the dipeptide **6**. This key intermediate was used as precursor of both the acid **7** (by reaction with (Bu₃Sn)₂O) and the amine **8** (under Staudinger conditions). Condensation of **7** and **8** gave the D-*alt*-L-tetrapeptide **9**.



Scheme 1. Synthesis of oligopeptides 6-10.

CONCLUSION

The sugar-based amino acid precursor **5** has been synthesized straightforward from D-Glucono-1,5-lactone. This building block was employed as key intermediate in the stereocontrolled synthesis of linear D-*alt*-L oligopeptides.

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