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Modification of Wang Resin and Macrocyclization in Solid-Phase Reaction

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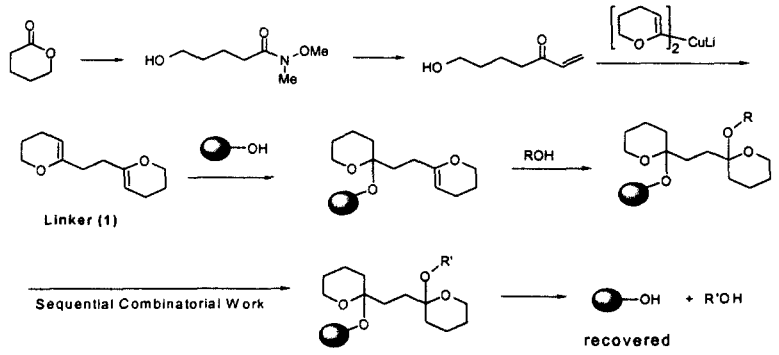
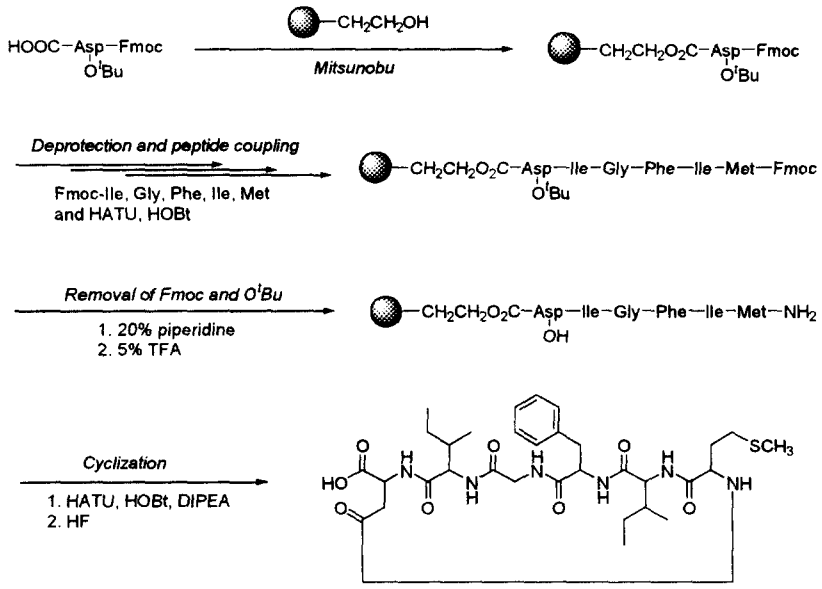
The linker which plays a role in connecting a polymer with a scaffold has become an important part in solid-phase reaction. To develop a new linker for alcohols and carbohyrates, dihydropyran moiety was selected in this study. New linker, 1-(4′,5′-dihydro-5*H*-pyranyl)-7-hydroxyheptan-3-one was synthesized via four steps from δ-valerolactone. This can be called as DDHP-linked Wang resin due to double dihydropyran rings. To the one pyran ring of new linker was added Wang resin and other alcohols and carbohydrates as scaffolds were then added successfully to the another pyana ring. Carbohydrate and hydroxyl resins were connected via new linker in a 70% loading yield. When certain combinatorial chemical works are carried out using this dihydropyran linker, Wang resin itself can be recovered. In another hand, we synthsized cyclic peptide using both solution-phase and solid-phase rection. We found that solid-phase reaction is efficient macrocyclization method (improvement from 3% to 35%). After the cleavage of linker, TentaGel resin was recovered in contrast to the other cyclization.



Scheme 1. Design of new dihydropyran linker and its synthetic strategy

We can see that there are many spotlights on peptide drugs by examining the recent trend in drug development. For example, drugs like cyclosporin shows striking activity as an autoimmune suppressor. Especially, cyclic peptides stands out among all other peptides as a good drug. That is why we are trying to develop more effective cyclization process.

There are three ways to cyclize certain sequences of amino acids such as Gly-Met-Ile-Phe-Gly. First is head-to-tail cyclization method, linking between N-terminal and C-terminal. Second method utilizes amino acid side chain such as thiol functional group in Cys, making a thioether bond. The last one includes an application of resin-substituted amino acids in solid phase reaction. Among the three methods, solid phase reaction showed the greatest yield.



Scheme 2. Synthesis of Cyclic Peptide in Solid-Phase