Synopsis of Original Research Paper

Design, synthesis and functions of self-assembled biomolecules.

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A synthetic method was developed for synthesizing α,α--disubstituted glycines bearing a large hydrophobic ring (more than 15-membered ring) based on ring-closing metathesis. Ring-closing metathesis reactions of the dialkenylated malonate precursors turned out to proceed efficiently, particularly when long methylene chains adequately tether both terminal olefin groups. Surprisingly, the amino groups of the α,α-disubstituted glycines bearing a large hydrophobic ring are inert to conventional protective reactions (e.g., N-Boc-protection: $Boc_2O/DMAP/CH_2Cl_2$; N-Z-protection: Z-Cl (benzyloxycarbonyl chloride)/$DMAP/CH_2Cl_2$). The Curtius rearrangement of the carboxylic acid functionality of the malonate derivatives, obtained after the ring-closing metathesis, to an amine functionality can be catalyzed by diphenylphosphoryl azide (DPPA), but unexpectedly, only the intermediate isocyanates can be isolated, even in the presence of alcohols such as benzyl alcohol. Thus, the corresponding isocyanates were isolated in high yields when this Curtius rearrangement was carried out in an aprotic solvent (benzene). The resultant isocyanate was treated with 9-fluorenylmethanol in a high boiling point solvent such as toluene under reflux to give the N-Fmoc-protected aminomalonate derivatives in high yield. These hydrophobic amino acids can be incorporated into a peptide by Fmoc-solid phase peptide synthesis using the acid fluoride activation method. In a 17-amino-acid peptide sequence known to take a monomeric α-helix structure, the replacement of two alanines with two new hydrophobic amino acids bearing a cyclic 18-membered ring enhanced the stability of the helical structure. Assembly to hexamers was also suggested by the results of sedimentation equilibrium studies in the presence of 100 mM NaCl.