A Combinatorial Strategy for the Synthesis of Various Amino Acid Derivatives of C_{60} and C_{70}

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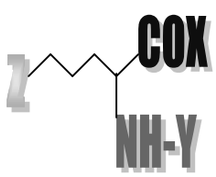
An original strategy was developed for the synthesis of numerous novel amino acid derivatives of C_{60}. This strategy is also applicable for the C_{70} fullerene. Using the extra functionality (-COOH, -OH or -NH_2) of the following polyfunctional amino acids Ser, Thr, Asp, Glu, Lys, Orn and hydroxy-Pro, novel compounds were generated by performing the "linking" chemistry electively on the free functional group, while the other groups were suitably protected. The functionalization reactions employed were Bingel cycloaddition and azide [3+2] dipolar addition. Our approach was driven by the necessity of developing water-soluble derivatives of C_{60} for pharmacological studies. Fullerene-based compounds demonstrated an interesting versatility in nitric oxide synthase inhibition and a subtle structure-function relationship depending on the nature of the polar head-group. We were interested in devising a strategy that will allow us to anchor addends with a similar skeleton but different hydrophilic groups. The L-amino acids Ser, Thr, Asp, Glu/Orn, Lys, HO-Pro represent a series of synthons characterized by a variable carbon chain structure and multiple functionalities, which provide ideal diversity elements. Moreover, the amino acid chirality offers the opportunity to use their D- enantiomeric counterparts as complementary building blocks. We focused initially on making zwitterionic free α-amino acids derivatives. The strategy was therefore directed in the first place at linking the amino acid residue in such a way that the proximal α-amino acid functionality will remain protected until the last step, when it would be deprotected, unmasking the water-solubilizing groups. We subsequently realized that the "three-way" format of the polyfunctional amino acids could be fully exploited in a combinatorial synthetic approach: by selecting the free functional group one at a time by "circular permutation" (while protecting the other two groups). In these latter cases, which we called "flipped I" and "flipped II" variants, the final deprotection step unmasks different free functional groups, compared to the parent (non-flipped) amino acid adduct. In the original non-flipped route, the *distal* carboxylic acid group is reduced to the corresponding alcohol, which is used further as the versatile synthon. After deprotection, this route generates a free, zwitterionic amino acid derivative (Fig. 2). In the "flipped I" variant, the *proximal* carboxyl is used in a similar fashion (Fig. 3). In the "flipped II" version, the free α-amino group is used as the linker, leading to polycarboxilic adducts. (Fig. 4). We generated several series of amino acid mono, bis- and tris-adducts of C_{60} and a few mono- and bis-adducts of C_{70}. The C_{60} bis-derivatives were obtained either via stepwise addition of malonates or azides or by tether-directed methods based on the *meta* or *para*-benzene-dimethanol scaffolds.



X: -OH, OtBu
Y : -H, -Boc
Z: -OH, -NH_2, -OtBu, -COOH, -COOtBu

Fig. 1. Schematic representation of the permutable synthon.

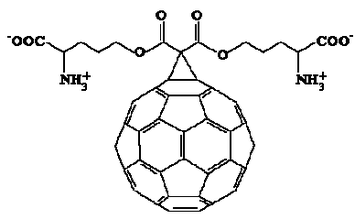


Fig.2 A zwitterionic α-amino acid

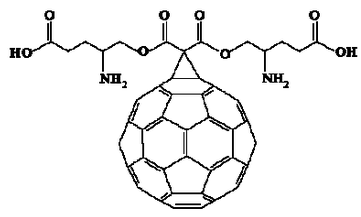


Fig.3 A γ-amino acid obtained from a flipped I derivative

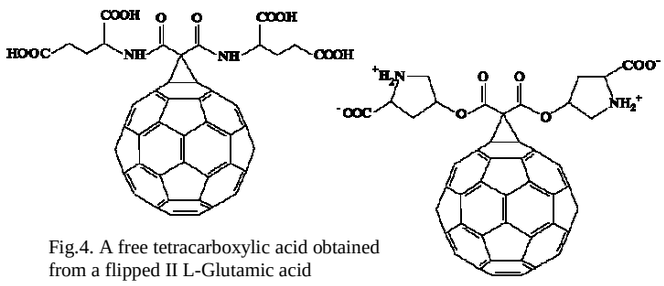


Fig.4. A free tetracarboxylic acid obtained from a flipped II L-Glutamic acid

Fig. 5. This straightforward route was also effective for the attachment of the heterocyclic moiety of imino acid Proline starting from N_{α}-Boc, -COOtBu protected hydroxy-Proline derivative (above-right as a bis-malonate monoadduct and below as a *cis-2* tethered bis-adduct).