# Addition Reactions of $C_{60}$ Leading to Fulleroprolines

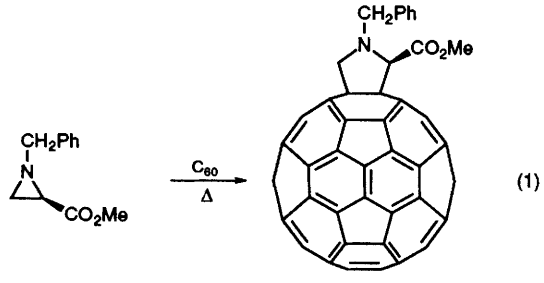
**Michele Maggini,[a] Gianfranco Scorrano,[a] Alberto Bianco,[a] Claudio Toniolo,[a] Rint P. Sijbesma,[b] Fred Wudl[b] and Maurizio Prato*[c]**

[a] *Centro Meccanismi di Reazioni Organiche and Centro di Studio sui Biopolimeri, CNR, Dipartimento di Chimica Organica, Università di Padova, Via Marzolo 1, 35131 Padova, Italy*
[b] *Department of Chemistry, University of California, Santa Barbara, CA 93106, USA*
[c] *Dipartimento di Scienze Farmaceutiche, Università di Trieste, Piazzale Europa 1, 34127 Trieste, Italy*

The synthesis of a series of racemic and enantiopure $C_{60}$-containing prolines is described.

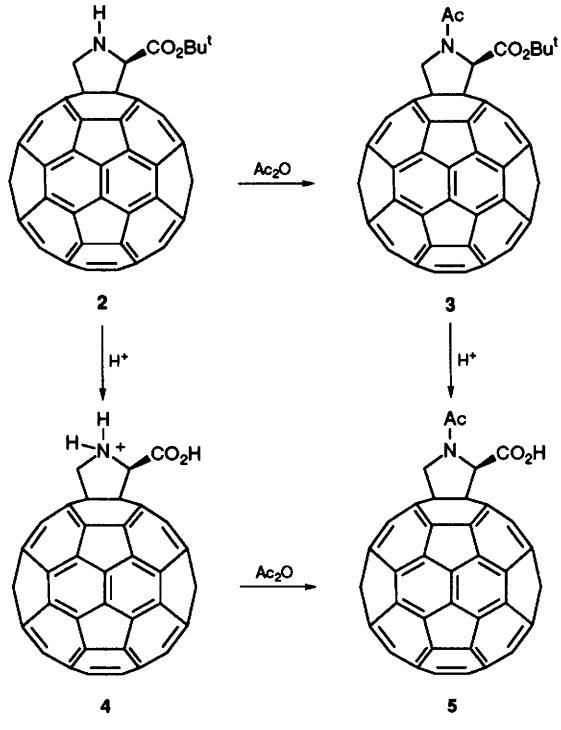
We have recently devised a new and general fullerene functionalisation, based on 1,3-dipolar cycloadditions to $C_{60}$. Azomethine ylides, generated in different ways, add to $C_{60}$ affording substituted fullerene–pyrrolidine in excellent yields.[1] Among other approaches, thermal ring opening of aziridines was employed and we obtained good yields of the fullerene 3,4-substituted proline **1** [eqn. (1)].

Recently, it was shown that a water-soluble derivative of $C_{60}$ interacts with the active site of HIV-1 protease,[2] indicating the potential role of fullerenes in medicinal chemistry. Here, we describe the preparation of some fullero-3,4-prolines and, in particular, of selected *N*-acetyl derivatives.




(1)

**1**




**2** **3** **4** **5**

Scheme 1

Although the *N*-benzyl and the methyl ester groups can be readily removed under mild conditions, **1** was not suitable for further elaboration, owing to the incompatibility of the fullerene sphere to either catalytic hydrogenation or alkaline hydrolysis.

The best route to the preparation of the unsubstituted fullero-3,4-proline was the reaction of glycine *tert*-butyl ester, paraformaldehyde and $C_{60}$ in refluxing toluene.† Fulleroproline *tert*-butyl ester **2** was formed but was found to be unstable, probably owing to the reactivity of amines with fullerenes.[3] However, **2** could be readily functionalised at nitrogen by treating the reaction mixture directly with acetic anhydride (Scheme 1). The stable acetamido derivative **3** was isolated in 32% yield (86% based on reacted $C_{60}$) and fully characterised.‡

When **2** was treated with trifluoromethanesulfonic acid in toluene at room temp., the protonated amino acid **4** (triflate salt) precipitated and was centrifuged and isolated in nearly quantitative yield. For further characterisation, **4** was allowed to react with acetic anhydride and pyridine to give the *N*-acetyl derivative **5**. The acetamido ester **3** could also be hydrolysed to **5** under the same acidic conditions (Scheme 1).

The high potential of **4** in peptide synthesis is evident. Fulleroproline **4** represents the first example of an amino acid linked directly to a fullerene. In principle, this compound may constitute a valuable building block for the construction of peptides containing $C_{60}$[4] that may have HIV-1 protease inhibitory properties.

To prepare optically pure substances a preliminary asymmetric azomethine ylide cycloaddition was carried out. The chiral 5,6-diphenylmorpholin-2-one **6**[5] was heated with chloromethyl octyl ether and triethylamine: the resulting *N*-octyloxymethyl derivative was added to a mixture of $C_{60}$ and *p*-toluenesulfonic acid to give the optically pure fulleroproline **7** in 26% yield (46% based on $C_{60}$ conversion).§

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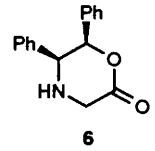
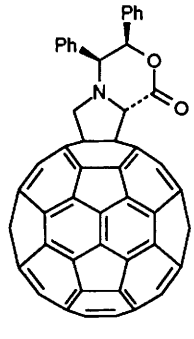
## Footnotes

† This approach represents the 'isomerisation route' to azomethine ylides: cf. ref. 6.




**6**




**7**

‡ The new compounds **3**, **5** and **7** showed correct analytical and spectroscopic data.
§ The absolute configuration of the newly formed chiral centre (Cα of proline **7**) was determined as *S* on the basis of NOE experiments.

## References

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