Synthesis and applications of 7-azabicyclo[2.2.1]heptane-1-carboxylic systems

José Ignacio Barriobero Neila

ABSTRACT

First, we have developed a versatile methodology to obtain a-amino ketones by acylation of methyl N-benzoyl-7-azabicyclo[2.2.1]-heptane-1-carboxylate with organolithium reagents. The reaction proceeds via a stable tetrahedral intermediate.

We have studied the versatility and synthetic potential of 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (Ahc) to obtain several bridgehead 1-substituted-7-azabicyclo[2.2.1]heptane derivatives, including halogen derivatives, via bridgehead radical reaction, proving the existence of the bridgehead radical in 7-azabicyclo[2.2.1]heptane systems. Moreover, we have obtained the interesting compound N-benzoyl-7-azabicyclo[2.2.1]heptane, a precursor of epibatidine.

We have studied the synthesis and biological evaluation of two new conformationally restricted ABT-418 analogues. This restriction is introduced by the incorporation of the 7-azabicyclo[2.2.1]heptane skeleton. Furthermore, we report high-level quantum mechanical study of their conformations in the gas phase.

Also, we have replaced the 4-hydroxyproline in the peptide Piv-4-Hyp-Gly-NHMe with the conformationally restricted hydroxyprolines exo-3-HyAhc and endo-3-HyAhc. These new amino acids induce changes on the peptide conformation. In these amino acids, the angle $\square_{i+1}$ decreases and the amides are not plane. These results could be useful to study the relationship between $\square$-turns and the biological activity of related compounds.

All four enantiomerically pure 2-hydroxy-7-azabicyclo[2.2.1]-heptane-1-carboxylic acids, four new enantiopure restricted analogues of 3-hydroxyproline, are described. The synthesis starts with the Diels–Alder reaction between methyl 2-benzamidoacrylate and Danishefsky's diene and uses as key steps a base-promoted internal nucleophilic displacement of the methanesulfonate group in the cyclohexane ring followed by a resolution method that involves formation of diastereomers and further separation by crystallization. This synthetic route allowed us to obtain both enantiomers of the *N*-Boc-7-azabicyclo[2.2.1]heptan-2-ones, valuable ketones used as precursors of (–)- and (+)-epibatidine or other more interesting analogues.

The retro-Dieckmann reaction has been used as a stereodivergent synthetic tool on *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one-1-carboxylic acid methyl ester to obtain enantiopure *trans*- and *cis*-5-(carboxymethyl)pyrrolidine-2-carboxylic acid methyl esters. These disubstituted pyrrolidines have been used as starting materials to develop concise and straightforward syntheses of all four stereoisomers of carbapenam-3-carboxylic acid methyl esters. In this way, we have confirmed unequivocally the stereochemistry of two carbapenams isolated from strains of *Serratia* and *Erwinia* species.

Universidad de La Rioja. Servicio de Publicaciones 2003 ISBN 84-688-4679-1