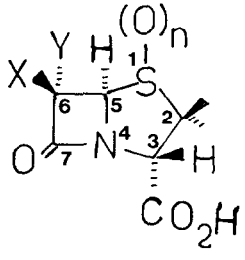
STEREOSELECTIVE SYNTHESIS OF 6-FLUOROPENICILLANIC ACIDS ANALOGUES OF β-LACTAMASE INHIBITORS.

E.G. Mata, G. Danelon, C.J. Salomon and O.A. Mascaretti

Instituto de Química Orgánica de Síntesis (CONICET-UNR)-Facultad de Ciencias Bioquímicas y Farmacéuticas Universidad Nacional de Rosario Suipacha 531, 2000 Rosario, Argentina.

Our primary interest in introducing a fluorine atom at specific sites of the penicillin molecule was due to the knowledge that replacement of hydrogen atoms in organic compounds by fluorine atoms will not have significant steric consequences at enzyme binding sites. However, fluorine with its very high electronegativity, will alter the acidity of geminal carbon 6 hydrogen and the acylatin reactivity of the vecinal β-lactam carbonyl group. Furthermore, the gem difluoro group ($-CF_2-$) has a steric profile similar to that of the methylene group but has a very different polarity and a drastically altered reactivity.

In this communication we will present the stereoselective synthesis of 6β-bromo-6α-fluoro- and 6β-fluoro-6α-bromopenicillanic acids (1a-b); 6β-fluoro- and 6α-fluoropenicillanic acids (2a-b); 6β-fluoro- and 6α-fluoropenicillanic acid 1,1-dioxide (3a) and (3b) respectively and our attempts of preparation of 6β-iodo-6α-fluoropenicillanic acid (4), 6,6-difluoropenicillanic (5) and 6,6-difluoropenicillanic acid 1,1-dioxide (6).



1a	X=Br	Y=F	n=0
1b	X=F	Y=Br	n=0
2a	X=F	Y=H	n=0
2b	X=H	Y=F	n=0
3a	X=F	Y=H	n=2
3b	X=H	Y=F	n=2
4	X=I	Y=F	n=0
5	X=Y=F		n=0
6	X=Y=F		n=2