Univerza
v Ljubljani

Fakulteta za kemijo
in kemijsko tehnologijo

p.p. 537, Večna pot 113
1001 Ljubljana
telefon: 01 479 80 00
faks: 01 241 91 44
dekanat@fkkt.uni-lj.si

VABILO NA PREDAVANJE
V OKVIRU DOKTORSKEGA ŠTUDIJA
KEMIJSKE ZNANOSTI

dr. Zdenko Časar

Lek Pharmaceuticals d.d., Sandoz Development Center Slovenia & Faculty of Pharmacy, University of Ljubljana

z naslovom:

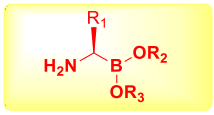
Synthesis of Chiral α-Amino Boronic Esters: Key Building Blocks of Proteasome Inhibitors

v sredo, 2. marca 2016 ob 15:00 uri
v predavalnici 1 v 1. nadstropju Fakultete za kemijo in kemijsko tehnologijo, Večna pot 113

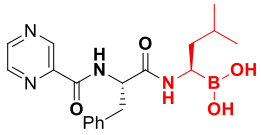
Vljudno vabljeni!

Povzetek:

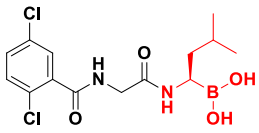
Chiral α-amino boronic esters serve as key precursors of proteasome inhibitors like bortezomib and ixazomib, which are approved and marketed drugs for treatment of multiple myeloma.



Chiral -amino boronic esters



Bortezomib
FDA approved in 2003
(Takeda/Millennium)



Ixazomib
FDA approved in 2015
(Takeda/Millennium)

Beside the above presented application in the field of medicinal chemistry, there are several other important aspects of chiral boronic esters applications. Indeed, chiral boronates represent valuable building blocks, which were till now prepared with limited number of synthetic methods. Moreover, halo substituted analogues like chiral (α-chloroalkyl) boronic esters are even more interesting chiral building blocks, which can be utilized in various coupling reactions and can undergo functional group transformation either at halogen substituent or at boron moiety (e.g. transformation to alcohols) giving a plethora of possibilities for their application in synthetic chemistry. They could be viewed also as "universal" chiral building blocks. Despite their broad applicability, chiral (α-chloroalkyl) boronic esters were until our discovery, highlighted in the present lecture, obtained only by Matteson´s homologation approach.

In the present lecture, primary and key modern synthetic approaches to chiral α-amino boronic esters and bortezomib will be presented. Then, discovery and some process optimization of asymmetric iridium-catalyzed chemoselective hydrogenation approach to chiral (α-chloroalkyl) boronic esters will be discussed. Firstly, synthesis of (1-chloro-1-alkenyl)boronic ester starting materials from commercially accessible alkynes will be presented. Subsequently, asymmetric hydrogenation of (1-chloro-1-alkenyl)boronic esters with iridium P^N-ligand based catalysts to chiral (α-chloroalkyl) boronic esters, which proceeds without substantial dehalogenation, will be described. In the final part, one-pot conversion of chiral (α-chloroalkyl) boronic esters to chiral α-amino boronic esters, featuring nucleophilic substitution with NaHDMS followed by the acid mediated hydrolysis of silyl protection, will be mentioned. Our method also demonstrated, for the first time, that homogenous catalyzed hydrogenation of vinyl halide type compounds can be performed chemoselectively without substantial dehalogenation, which was before considered as an unachievable goal in synthetic chemistry.