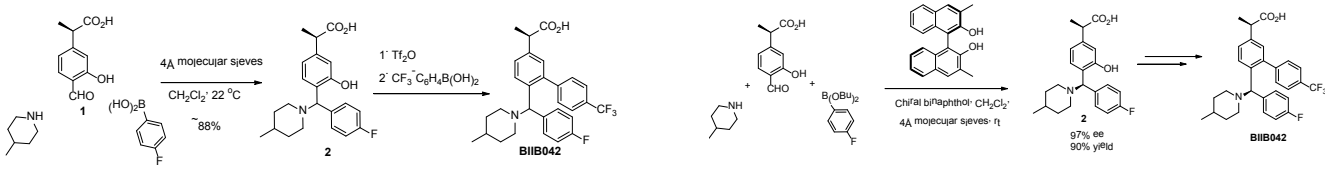
Xianglin Shi, Med Chem (Los Angeles) 2017, 7:8(Suppl)
DOI: 10.4172/2161-0444-C1-033

Development of novel Petasis reaction methodologies for efficient and scalable synthesis of biologically interesting compounds

Xianglin Shi
Chemical Process R&D, Biogen Idec, USA

BIIB042, a αγ-secretase modulator, was pursued for its potential in the treatment of Alzheimer's Disease. Med. Chem. synthesis consisted of four chemical reactions. A mixture of four diastereomers were made in the first step and carried through to the end of the synthesis. BIIB042 was obtained in ~4% overall yield via chiral HPLC separation. A seven-step process was developed for delivery of kilograms of BIIB042. A racemic mixture made in the first step was separated using SMB chromatography. Second chiral center was introduced in the last step by stereoselective hydrogenation reaction to afford BIIB042 in 95-96% ee. This route afforded the API in ~9% overall yield. Further improved synthesis included synthesis of **2** by Petasis reaction of enantioenriched aldehyde **1** followed by its conversion into BIIB042 in two steps. Development of a mild and efficient Petasis reaction condition made synthesis of **2** in high yield without loss of ee possible. This new Petasis reaction condition was applicable to a variety of substrates. A catalytic asymmetric Petasis reaction was then developed to synthesize 2 in 97% ee at the newly generated stereogenic center and ~90% yield (Scheme 2). This completed asymmetric synthesis of **BIIB042**. This catalytic asymmetric Petasis reaction methodology has been demonstrated with a variety of secondary amines, salicylaldehyde derivatives, and (alkenyl)$B(OBu)_2$ (Shi, X. et al. *J. Org. Chem.* **2013**, 78, 9415) and arylboronates (*manuscript in preparation*). During the mechanistic studies by NMR, we observed a catalytic effect of amines on transesterification reaction of boronates with the binaphthol catalysts (Scheme 3). The uncatalyzed transesterification reaction, however, seemed to be accepted as the first step for binaphthol catalyzed reactions of boronates with iminium ions (Petasis reaction), conjugated ketones, lactol (cyclic hemiacetala), and acylimines.



Biography

Xianglin Shi received a B.S. in chemistry from Yanan University and an M.S. under the direction of Prof. Yuqun Chen from Shanghai Institute of Organic Chemistry, the Chinese Academy of Sciences, China. After teaching chemistry in Yanan University for six years, he was admitted to Auburn University, Auburn, Alabama, where he completed his M.S. under the direction of Prof. Peter Livant. He then went on to Emory University, Atlanta, Georgia for his Ph.D. under the direction of Prof. Lanny S. Liebeskind and received his Ph.D. in 2000. He began his industrial process chemistry career in 2000 at Rhodia Chirex, Boston, where he was the leading chemist for the development of several chemical processes. In 2003, he joined the Process Research group at Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts. He held positions of increasing responsibility in process R&D and scale-up for drug intermediates and candidates in early and late stage development. Since 2006, he has been a senior and principal scientist in the process chemistry group for small molecules at Biogen, Cambridge, Massachusetts and been involved in process R&D, scale-up, and CMC activities. Recently, he has been engaged in oligonucleotide API process development, validation, CMC, and Spinraza worldwide NDA. He is responsible for the oligonucleotide synthesis process development and scale-up for manufacturing.

xianglin.shi@biogen.com

Notes: