

Jew*

College of Pharmacy, Seoul National University, Seoul 151-742, South Korea

A trimeric Cinchona alkaloid ammonium salt, a,a',a''-tris[O(9) allylcinchonidinium]mesitylene tribromide has been prepared as a novel phase-transfer catalyst. The catalytic enantioselective alkylation of N-(diphenylmethylene)glycine tert-butyl ester using the trimeric catalyst show high enantioselectivity (90 ~ 97% ee).

[PD1-14] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Novel Asymmetric Synthesis of (1R, 2S)-1-Allyl-2-Silanyloxy Carbamates as precursors for the Synthesis of β -Hydroxy- α -Amino Acids using CSI reaction

Kim JD^o, Jung YH

College of Pharmacy, Sungkyunkwan University

β -Hydroxy- α -amino acids are an important class of compounds due to their inherent biological activities and their role as structural components of more complex organic compounds that possess a wide range of biological activities, such as antifungals, antibiotics and immunosuppressants. They are also useful intermediates in the synthesis of other compounds, such as β -lactams, aminosugars, chiral ligands and β -fluoro amino acids. So, a number of elegant approaches have been described for the asymmetric synthesis of various β -hydroxy- α -amino acids in enantiomerically pure form. We have recently described synthetic method for N-protected allylic amines from allyl ethers using chlorosulfonyl isocyanate(CSI) via the stable allylic carbocation. In this presentation, we will report novel asymmetric synthetic method for (1R, 2S)-1-allyl-2-silanyloxy carbamates as precursors for the synthesis of β -hydroxy- α -amino acids by the simple CSI reaction which we developed with various allyl ethers and discuss mechanism of these reactions.

[PD1-15] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Microbial asymmetric reduction of β -keto ester for the synthesis of 4-acetoxazetidinone

Lee J^o, Yoon HC

R & D Center, Daewoong Pharm. Co., Ltd., 223-23 Sangdaewon-dong, Joongwon-gu, Sungnam, Kyunggi-do 462-120, Korea

A chiral compound, 4-acetoxazetidinone is considered as the key intermediate for the preparation of β -lactam antibiotics such as carbapenems or penems. We investigated the microbial asymmetric reduction of ethyl 2-(phthalimidomethyl)acetoacetate as β -keto ester substrate by bacteria and fungi as well as yeasts expecting the production of (2S, 3R)-ethyl 2-(phthalimidomethyl)-3-hydroxybutyrate (syn-1) according to the anti-Prelog rule. We report here the screening results of microbial asymmetric reduction carried out with 465 species of microorganisms according to the conventional screening method. All reaction products were analysed with HPLC and screening results were discussed in detail.

We can expect the production of four stereoisomers, two syn- and two anti-isomers resulted from microbial asymmetric reduction. Therefore, four isomers (syn-1, syn-2, anti-3 and anti-4, respectively) were prepared by NaBH₄ reduction of ethyl 2-(phthalimidomethyl) acetoacetate and identified by HPLC with chiral column. Although most microorganisms produced one syn-isomer (syn-2) and two anti-isomers generally, 10 species showed characteristic product distribution in which main product was (2S, 3S)-ethyl 2-(phthalimidomethyl)-3-hydroxybutyrate (anti-4) corresponding to

Prelog rule. From these results, it is expected that these microorganisms will be applicable to prepare (S)-isomer of the secondary alcohol in the future. Finally, it was found that one yeast produced (2S, 3R)-isomer (syn-1), which is the rare instance in the asymmetric reduction of β -keto ester.

[PD1-16] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Design and Synthesis of the Highly Selective Inhibitors of Type IV Collagenase(MMP-2 and MMP-9) of Benzthiazolesulfonamide Derivatives III

Min HK, Kim KC, Bae HY, Ryu CH, Lee JW, Paek SH, Park YJ, Chae MY, Park MJ, Shin HC, Yoo JU

drug Discovery Lab, Samsung Advanced Institute of Technology, Korea Research Institute of Chemical Technology, Taejon

Matrix metalloproteinases (MMPs) are a family of Zinc endopeptidase that are capable of hydrolyzing the extracellular matrix of connective tissues and basement membranes. Although their roles in the normal and pathological turnover of these tissues are not completely understood, the elevated levels of these enzymes, particularly MMP-3 and MMP-1, found in the synovium and cartilage of rheumatoid arthritis patients have suggested a role for these enzymes in this disease process. MMP-2 and MMP-9 are particularly proficient at degrading basement membranes and are thought to play a role in tumor metastasis and angiogenesis.

We have focused on the discovery of potent, selective, and oral absorptive inhibitors of MMP-2/MMP-9. By structure-activity relationship studies and structural analysis, we have discovered that 2-alkyl, arylthio-6-benzthiazolesulfonyl moieties are very useful substituent for S1'sub-site in enzymes. Various inhibitors are synthesized by the reaction of a novel unnatural amino acid with 2-alkyl, arylthio-6-benzthiazolesulfonyl chloride and determined the biological activities. Many benzthiazolesulfonamide inhibitors have a potent inhibitory activity with the IC50 value of nM against MMP-2/MMP-9 along with very good selectivity against MMP-1 and some inhibitor has a good pharmacokinetic profile.

In this meeting, we will discussed the design, synthesis, and activity of the highly selective inhibitors of MMP-2 and MMP-9.

[PD1-17] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Design and Synthesis of the Highly Selective Inhibitors of Type IV Collagenase(MMP-2 and MMP-9) of Benzthiazolesulfonamide Derivatives II

Kim KC, Min HK, Bae HY, Ryu CH, Lee JW, Paek SH, Park YJ, Chae MY, Yoo JU

Drug Discovery Lab, Samsung Advanced Institute of Technology, Taejon

Matrix metalloproteinases (MMPs) are a family of Zinc endopeptidase that are capable of hydrolyzing the extracellular matrix of connective tissues and basement membranes. Although their roles in the normal and pathological turnover of these tissues are not completely understood, the elevated levels of these enzymes, particularly MMP-3 and MMP-1, found in the synovium and cartilage of rheumatoid arthritis patients have suggested a role for these enzymes in this disease process. MMP-2 and MMP-9 are particularly proficient at degrading basement membranes and are thought to play a role in tumor metastasis and angiogenesis.

We have focused on the discovery of potent, selective, and oral absorptive inhibitors of MMP-2/MMP-9. By structure-activity relationship studies and structural analysis, we have discovered that 2-alkyl, arylthio-6-benzthiazolesulfonyl moieties are very useful substituent for S1'sub-site in enzymes. Various inhibitors are synthesized by the reaction of a novel cyclic D-amino acid with 2-alkyl, arylthio-