[PD1-11] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Synthetic Approach to Natural Antioxidants: Benzastatin E, Benzastatin F and Benzastatin G

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Benzastatins (E, F, G) that contain indoline skeleton are three of seven compounds isolated from culture broth of Streptomyces nitrosoporeus. Benzastatins (E, F, G) have been reported as first natural indoline derivatives to show inhibitory activity against glutamate toxicity and strong antioxidant activity (lipid peroxydation inhibition in rat liver microsomes). Aiming at the structure-activity relationship study and development of antioxidants, we tried to synthesize benzastatins (E, F, G) and their analogues. We report here the synthetic method of indole structure via cyclization of ethyl-3-(2-nitrophenyl)-2-propeonate with/without substituent at 5 position and attempts to synthesize alkene side chain of benzastatins (E, F, G).

[PD1-12] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Design and Synthesis of fluorocyclopropanoid Nucleosides

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Novel fluorocyclopropanoid nucleoside analogues with three fuctionaliti-
es were designed and synthesized. First, cyclopropyl group possesses a hybrid character of acyclic chain and carbocyclic moiety and controls the conformation. Second, hydroxymethyl group was introduced for phosphorylation. And finally, fluorine mimics the electronic effect of the oxygen of natural nucleosides and controls the confromation by Gauche effect between fluorine and nitrogen of base.
The key intermediate, (±)-(E/Z)-[2-(tert-butyldiphenylsilanyl-oxymethyl)-1-fluorocyclopropyl] methanol was synthesized by the Lewis acid-
catalyzed Furukawa method of Simmon-Smith reaction starting from allyl alcohol. The fluorinated ester with E/Z configuration was synthesized as a major product by Horner-Wadsworth-Emmons olefination.
Mesylate or iodide was coupled with adenine, 2-amino-6-chloropurine, cytosine and thymine under NaH, K2CO3, Cs2CO3 and DBU conditions and resulted in novel (±)-(E/Z)-(1`-fluoro-2`-hydroxymethy-cyclopropylmethyl)purine analogues and pyrimidine analogues.

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

Trimeric cinchona alkaloid phase-transfer catalyst: a,a',a"-Tris[O(9)-allylcinchonidinium]mesitylene tribromide

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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

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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 immunosuppresants. 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 elegants 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-acetoxyazetidinone

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A chiral compound, 4-acetoxyazetidinone is considered as the key inter-mediate for the preparation of β-lactam antibiotics such as carbapenems or penems. We invesgated 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 charac-teristic 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

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Matrix metalloproteinases (MMPs) are a family of Zinc endopeptidase that are capable of hydrolyzing the extracelluar 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 extracelluar 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-

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 discuss the design, synthesis, and activity of the highly selective inhibitors of MMP-2 and MMP-9.

[PD1-18] [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 I

Bae HY, Min HK, Kim KC, 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 extracelluar 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 simple amino acid with 2-alkyl, arylthio-6-benzthiazolesulfonyl chloride and determined the biological activities.
In this meeting, we will discuss the design, synthesis, and activity of the highly selective inhibitors of MMP-2 and MMP-9.

[PD1-19] [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 Biphenylbutyric Acid Derivatives

Ryu CH, Min HK, Kim KC, Bae HY, 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 extracelluar 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, we found that N-substituted-5-(biphenyl-4-yl)-5-oxo-3-carboxylvaleric amide derivatives exhibited inhibitory activity with the IC50 value of nM against MMP-2 and some inhibitor has a good pharmacokinetic profile.
In this meeting, we will discuss the design, synthesis, and activity of the highly selective inhibitors of MMP-2 and MMP-9.