Studies Toward the Total Synthesis of Pancratistatin, Anticancer Natural Product

Ko Hyojin°, Kim Eunkyung, Kim Sanghee*

Natural Products Science Research Institute, Seoul National University

The Amaryllidaceae alkaloid pancratistatin was first isolated from the roots of Pancratium littorale in 1984. The promising biological activity as an anticancer agent and low natural abundance have made it an attractive target for total synthesis. The major challenge to synthesis include elaboration of the fused BC ring system and the stereoselective installation of the hydroxyl groups located around C ring. We wish to reporte on the successful synthesis of highly advanced intermediate of pancratistatin from a simple starting material utilizing Claisen rearrangement, Curtius rearrangement and cyclic sulfate chemistry as key steps to construct the fused BC ring system and introduce the hydroxyl groups on C ring.

[PD1-24] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

New approach to the synthesis of (+)-Lauthisan by stereoselective alkylation

Beom HY, Rhee HJ°, Kim HD

College of Pharmacy, Sookmyung Women's University

For the enantioselective synthesis of (+)-*cis*-Lauthisan and (-)-*cis*-Lauthisan, we designed and synthesized 2-[1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-trimethylsilanyl-allyloxy]-oct-4-enoic acid tert-butyl ester as a novel chiral auxiliary for optically active(+),(-)-*cis*-Lauthisan. The design of the chiral auxiliary was based on the postulated that a tridentate chelate formed by complexation of basic groups (two oxygens) on the auxiliary and metal cation bonded to ester enolate anion should efficiently shield one of the two diastereotopic faces of the enolate.
In connection with the synthesis of marine products and their analogues as potential antibiotics, we evaluated the chiral auxiliary as a synthetic tool for optically active (+)-*cis*-Lauthisan and (-)-*cis*-Lauthisan as a key step. The chiral auxiliary was alkylated with various kind of electrophiles via corresponding ester enolate generated by lithium hexamethyldisilazane at -78℃. D-Mannitol as achiral synthon was converted to 5-Ethyl-3-hexyl-6-hydroxymethyl-[1,4]dioxan-2-one through 6 steps.
In summary, we developed a novel synthetic method for optically active lactone, a key intermediate for (+),(-)-*cis*-Lauthisan. Taking into account of chiral auxiliary's chemical reactivities and selectivities, our method offer the fascinating possibilities for the development of new strategies for the optically active synthesis of natural marine products having 8-membered oxocane skeletons.

[PD1-25] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Effects of furanocoumarins isolated and semi-synthesized from the root of Angelica duhurica on NO and PGE2 production in murine macrophages

Lim SS[1]°, Jung SH[1], Ban SH[2], Kim YP[2], Shin KH[1], Ohuchi K[2]

[1]Natural Products Research Institute, Seoul National University, 28 Yeungun-dong, Jongro-gu, Korea, [2]Laboratory of Pathophysiological Biochemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Japan

Six furanocoumarins and related compounds isolated from the roots of Angelica dahurica ("Byak ji" in Korean) and the compound, selectively reduced from the major component, byakangelicin, were evaluated for their effects on NO and PGE_2 production in rat peritoneal macrophages induced by

lipopolysaccharide (LPS). The results showed that most of compounds except 2',3'-dihydrobyakangelicin, reduced form of furan double bond in byakangelicin, inhibited weakly or moderately NO production. But, in case of the PGE_2 production, imperatorin, isoimperatorin, phellopterin, isooxypeucedanin and 2',3'-dihydrobyakangelicin exhibited potent inhibition of PGE2 production. Western-blot analysis revealed that 2',3'-dihydrobyakangelicin inhibited the expression of the inducible forms of cyclooxygenase (COX-2) protein in concentration dependent manner.

[PD1-26] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

New Cephalosporin Antibiotics with (5-Substituted-Isoxazol-3-yl)-3-Pyridiniummethyl Derivatives.

Chang KY, Kwon SH, Kim SH,Nam GS, Seo JH, Choi KI, Kim JH, Ha DC

Biochemicals Research Center, Korea Institute of Science and Technology. Department of Chemistry, *Korea University*

The new cephalosporins with 3-isoxazolylpyridinium moiety exhibited well-balanced broad spectrum against Gram-positive and Gram-negative bacteria.
We found a moderate activity against Gram-positive and Gram-negative bacteria for simplified compound (1a), with unsubstituted isoxazole ring. The introduction of amino group (1b) beared fruitful *in improving the antibacterial activity against* Gram-positive and Gram-negative bacteria including P. aeruginosa. Activity of 1b exhibited similar to that of cefpirome.
The effect of substituents of heterocyclic ring to influence antibacterial activity against Gram-positive and Gram-negative bacteria should provide an important utility to the antibiotics arena

[PD1-27] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

New Cephalosporin Antibiotics with (5-Substituted-4,5-Dihydroisoxazol-3-yl)-1-Methyl-1,2,5,6-Tetrahydro-3-Pyridiniummethyl Derivatives

Chang KY, Kwon SH, Kim SH, Nam GS, Seo JH, Choi KI, Kim JH, Ha DC

Biochemicals Research Center, Korea Institute of Science and Technology. Department of Chemistry, Korea University.

The various (5-substituted-4,5-dihydroisoxazol-3-yl)-1-methyl-1,2,5,6-tetrahydro-3-pyridine derivatives possessing hydroxy, methyl hydroxy, alkoxy, methylthioether, thiophenyl group at the 5 position on 4,5-dihydroisoxazole ring were synthesized. These (5-substituted-4,5-dihydroisoxazol-3-yl)-1-methyl-1,2,5,6-tetrahydro-3-pyridine derivatives were coupled with cephalosporin moiety to produce new series of cephalosporin antibiotic and their antibacterial activity was inspected.
On the selected functionality of these SAR, 7-[(Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino) acetyl]amino-3-[5-hydroxy-4,5-dihydroisoxazol-3-yl-(1-methyl-1,2,5,6-tetrahydro-3-pyridinio) methyl]-ceph-3-em-4-carboxylate can be regarded as the best compounds, when compared the others, showing a better balances between Gram- positive and Gram-negative bacteria. 4,5-dihydroisoxazol-3-yl-(1-methyl-1,2,5,6-tetrahydro-3-pyridiniummethyl cephalosporin with thiopheny substituents beared fruitful in improving the activity against Gram-positive bacteria.

[PD1-28] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Simulation for Effect of p3 Segment on Aggregation of Amyloid Peptide Using Cellular Automata