

The vicinal amino alcohol moiety is a common structural component in a vast group of naturally occurring and synthetic molecules. The presence of this moiety and the relative stereochemistry are generally important for the biological activity of molecules containing a vicinal amino alcohol. As such, a variety of stereoselective synthetic methods have been developed. Just as there are an equally large number of synthetic routes to these molecules. Conceptually one can divide these synthesis into four different classes: (1) functional group manipulation of a molecule containing both heteroatoms, (2) addition of one heteroatom to a molecule which already contains one heteroatom, (3) addition of both heteroatoms to a molecule which has neither, (4) coupling of two molecules, each of which has one heteroatom. We have recently described synthetic method for N-protected allylic amines from allyl ethers using chlorosulfonyl isocyanate(CSI) via the stable allylic carbocation, and furthermore, we developed novel technique to compare directly the stability of carbocations in the solution phase using CSI reaction. In this presentation, we will report diastereoselective synthetic method for 1, 2-aminoalcohols by the our CSI reaction system and discuss mechanism of these reactions.

[PD1-15] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Asymmetric synthesis of (2S, 3R, 4E)-2-Amino-5-phenyl-pent-4-ene-1,3-diols

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(2S, 3R, 4E)-2-Amino-5-phenyl-pent-4-ene-1,3-diols had been stereoselectively synthesized. (1S, 5S)-(-)- α -Pinene was treated with KMnO₄ to give (1R, 2R, 5R)-(+)-2-hydroxy-3-pinane, which reacted with ethylglycinate, boron trifluoride etherate and then with C₆H₅CH=CHCHO, arylpropenal to yield (1R, 2R, 5R)-aldol compounds. These compounds were hydrolyzed with HCl and reduced with NaBH₄ to give (2S, 3R, 4E)-2-amino-5-phenyl-pent-4-ene-1,3-diols.

[PD1-16] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

A synthesis of novel acyclic nucleosides

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The discovery of acyclovir as an antiherpes agent ignited the search for new antiviral nucleosides with disconnected chain resulting from omitting any bond from the pentose or cyclopentane rings. During the last twenty years, many new synthetic schemes for various acyclic nucleoside analogues have been discovered and many of these molecules have shown promising antiviral activities. Among them, desciclovir, ganciclovir, penciclovir, famciclovir have shown potent antiviral activity against HBV and herpes virus. It could be assumed that the potent antiviral activity be originated from flexible acyclic sugar mimicking chain moiety. In view of these promising results of acyclic nucleosides and as part of our continuing drug discovery efforts, we planned to synthesize novel disecocnucleosides (two bond disconnection). Here, we would like to report the synthetic route of novel 1',x and 4',x-diseco-nucleosides from D-lactose.

[PD1-17] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Synthesis and Anti-Inflammatory Activity of Heteroaryl Substituted Flavones

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The flavonoids are a very large and important group of polyphenolic natural product, which exhibit a wide range of biological properties. To decipher the relationship between the structural modification of flavone B ring moiety and anti-inflammatory activity, we synthesized flavone analogs substituted with a heteroaryl group at the B ring position.

2'-Hydroxyacetophenone was reacted with various heteroaromatic aldehydes in alcoholic KOH to produce chalcones in good yields. Reactions in iodine-DMSO conditions provide a large number of synthetic flavones as crystalline products. The preparation of these products along with their anti-inflammatory activity will be discussed.

[PD1-18] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Peptidyl 2-Ketoimidazole Libraries for Protease Inhibitors

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Recently, it has been reported that 2-ketoheterocycles, electrophilic ketones, generate the transition-state mimetic in the process of proteolysis. Therefore, it is suggested 2-ketoheterocycles exhibit reversible mode of inhibition on serine proteases. We designed and prepared 2-ketoheterocycle libraries for the discovery of potent and specific protease inhibitors.

In the synthesis of tetra-peptidyl 2-ketoimidazole libraries (P4-P3-P2-P1-ketoimidazole), 2-ketoimidazole was obtained by the reaction of Weinreb amide originated from several natural and unnatural amino acids with 2-lithiated 1-methylimidazole in high yield. In order to obtain the peptidyl 2-ketoimidazole libraries, the parallel solution phase synthetic method was used for the introduction of various P2, P3, and P4 building blocks. We synthesized approximately 600 compounds being 2-ketoimidazole with diverse residues on P1~P4, and used this library for the discovery of serine protease inhibitors, such as HCV NS3 protease and elastases, etc.

[This study was supported by a grant of the National R&D Program, Ministry of Science & Technology, Korea (CH1-3-12)]

[PD1-19] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Stereocontrolled synthesis of novel 6'(β)-hydroxy-carbocyclic nucleosides

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Since 6'-hydroxymethyl substituted carbovir showed good biological activity as potent anti-HIV agent, many medicinal chemists started to explore 6'-modified carbocyclic nucleosides. Unfortunately, most of the known 6'-modified carbocyclic nucleosides have been synthesized as racemic mixture, probably due to the synthetic difficulties. Therefore enantiomeric synthesis of the novel 6'-substituted carbocyclic nucleosides would be synthetic challenging and biologically interesting. Furthermore, the recent approval of abacavir by FDA as an anti-HIV agent strongly warranted the further exploration of carbocyclic nucleosides as chemotherapeutic agents.

On the other hand, much attention has been paid to unnatural L-nucleosides since some of the L-enantiomers have been shown to possess more improved biological profiles than its D-counterpart. Among them, 3TC, FTC, L-FddC, L-FMAU were reported to be the promising antiviral agents. For example, L-FMAU showed greater potency against HBV and lower toxicity than D-FMAU. Recent approval of 3TC by Food and Drug Administration for the treatment of HIV and HBV infected individual shows the therapeutic significance of L-nucleosides.

In line with these interesting observations and as part of our ongoing drug discovery efforts, we have designed novel nucleosides with hydroxy group at 6'(β)-position of L-carbocyclic nucleosides that would hybrid the properties of 2',3'-dideoxy carbocyclic nucleosides and L-nucleosides. Herein, we would like to present an enantiomeric synthetic route of novel 6'(β)-hydroxy-2',3'-dideoxy-L-carbocyclic nucleosides, of which stereochemistry was successfully controlled by sequential chelation controlled Claisen