High enantioselective synthesis of novel 3'-C-methyl apio and thioapionucleosides:an asymmetric elaboration of a quaternary carbon by Claisen rearrangement

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Emerging drug-resistant virus strains as well as toxicity are major problems in antiviral chemotherapy. Therefore, a number of structurally modified nucleosides have been synthesized to overcome these drawbacks. Among the compounds synthesized, 4'-cyanoyhymidine, 4'-azidothymidine and 4'-fluoronucleosides are of particular interest as they represent a new class of compound and exhibit significant biological activity. Furthermore, more fundamental modification of pentofuranose moiety, such as isonucleosides and apionucleosides, have been reported to be compatible with antiviral activities. In attempts to find new lead antiviral compounds with improved biological activity, we have synthesized a number of apionucleosides and their thionucleosides using Claisen rearrangement with high enantiomeric excess (98.5% ee). We would like to present the synthetic procedure and their biological activity in the symposium.

[OD-2] [04/20/2001 (Fri) 13:45 - 14:00 / Room 3]

Syntheses and Structure-Activity Relationships of Pyrido[2,3-d]pyrimidine-2,4-diones as Phosphodiesterase 4 (PDE 4) Inhibitors.

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Synthesis of new pyrido[2,3-d]pyrimidine-2,4-dione analogues having substituent at C-3 and C-4 position on pyridine ring was accomplished by using simple and convenient Heck-coupling reaction in moderate yields. The biological activity of the compounds synthesized was evaluated as PDE 4 enzyme inhibition effect and the affinity to high affinity rolipram binding site (HARBS) through the rolipram binding assay. Some compounds exhibited better activity and selectivity than that of SB-207499, a promising drug candidate in phase III.

[OD-3] [04/20/2001 (Fri) 14:00 - 14:15 / Room 3]

Efficient syntheses of the versatile intermediates for the synthesis of D- and L-carbocyclic nucleosides

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D-Neplanocin A and D-aristeromycin are natural carbocyclic nucleosides which show promising antiviral and antitumor activities. However, despite of these interesting biological activity, their structure-activity relationship studies have been limited because of the synthetic difficulties in getting the key intermediate, D-cyclopentenone. Previously published syntheses of this intermediate suffer from low overall yields, many steps and etc. Since we have been interested in structure-activity relationship of these carbocyclic nucleosides, we have completed the efficient syntheses of this intermediate using ring closure methasesis (RCM). Synthesis of the D-cyclopentenone was started from erythrono-gamma-lactone. Reduction of the lactone to lactol followed by treating with vinyl magnesium bromide gave vinyl diol. Vinyl diol was oxidized to the vinyl lactol which underwent Wittig reaction to give divinyl derivative. Ring closure methasesis (RCM) of divinyl derivative followed by