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

allylic oxidation afforded D-cyclopentenone. Since many L-nucleosides have shown interesting biological activity, we also synthesized L-cyclopentenone using similar RCM strategy. Our syntheses were found to be superior to those of the previously published syntheses.

[OD-4] [04/20/2001 (Fri) 14:15 - 14:30 / Room 3]

Docking Study of Topoisomerase I - DNA Complex with 3-Arylisoquinolines

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DNA topoisomerase 1 is an essential enzyme for relaxation of DNA during a number of critical cellular processes, including replication, transcription, and repair. Topo I catalyzes change in the linking number of DNA by breaking and resealing phosphodiester bonds. Therefore, the enzyme is a cellular target for anticancer drug development, and the characterized topo I inhibitors are camptothecin and its derivatives. During our study for the finding of new anticancer agents, several isoquinoline derivatives were found to show very potent topo I poison. Docking experiments using Sybyl 6.6 were undertaken with topo I ?DNA complex structure and several isoquinoline compounds. This study provides a three-dimension model for the postulated ternary cleavable complex of topo I, DNA, and the ligand molecules. In this proposed ?drug-stacking model, the compounds are intercalated in the topo I 뿢inked DNA cleavage site and interacts with the thymine 11 and Lys 532.

[OD-5] [04/20/2001 (Fri) 14:30 - 14:45 / Room 3]

Biosynthesis of Ginseng Saponin(1): Determination of Protopanaxadiol and Protopanaxatriol in Panax ginseng hairy roots by ELISA methods

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Protopanaxadiol (PPD) and protopanaxatriol (PPT) were known as aglycones of dammarane type saponin, ginsenosides from *Panax ginseng* C. A. Meyer. As a course of investigating biosynthetic enzymes of dammarane ginsenosides, production of the aglycones was examined in *Panax ginseng* hairy roots by ELISA methods.
For this study we developed ELISA methods for measuring PPT and PPT using polyclonal antibody. In present study, we report: 1) A specific and sensitive ELISA was developed for the determination of PPD, and 2) PPD and PPT contents in *Panax ginseng* hairy roots were measured successfully. The Abs were obtained from rabbits by immunization with IH-901-bovine serum albumin conjugate was used as immunogen. While the Abs were found to be specific to both IH-901 and PPD, they showed minor or even no corss-reactivity to PPT (1.79%) and other ginsenoside tested (G-Rg_1:0.08%; G-Rb_1:0.13%; G-F_1:1.48%). The working range of the assay was from 0.025ng/well to 1.25ng/well. The comparison of ELISA and HPLC showed a good correlation (r=0.986) between the two methods.
In *Panax ginseng* hairy roots cultures (1/2 MS liquid medium; ca. 10 mg inoculum; 50ml/100ml flask; rotated at 100 rpm), both PPD and PPT contents were increased from the day 25. In conclusion, the ELISA methods could be very useful tools for the studies on the biosynthesis of dammarane glycoside.

[OD-6] [04/20/2001 (Fri) 14:45 - 15:00 / Room 3]

Isolation of HIV gp-41 Binding Components from the Stem of Fraxinus sieboldiana