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Costunolide which is known as a chemopreventive drug is a sesquiterpene compound isolated from Magnolia Sieboldii. and has antitumor and antiinflamatory activities. it is very hard to collect enough amount of natural extracts of costunolide for the activity studies. therfore, synthesis of costunolide derivatives is honestly needed. the aim of this research is to develope new methods for costunolide synthesis and to test biological activities. two diffrent macrocyclization methods were applied : application of a low-valent chromium reagent for the construction of the germacrane-skeleton from the linear precursor. this application already was carried out and we got a small amount of costunolide : application of selenium reagent for the construction of the same moiety

[PD1-63] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Chiral Synthesis of Costunolide

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Costunolide, a sesquiterpene lactone is isolated from Magnolia Sieboldi. It is known to possess antitumour and anti-inflammatory activities. This compound is synthesized from the easily available decalin dione using the ring cleavage approach to construct the ten-membered ring system. The two keys points in this work are the chiral induction on the allyl alcohol moiety using Sharpless epoxidation reaction, and opening of the epoxide with an organocuprate reagent which leads to a α-exomethylene lactone.

[PD1-64] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis and Biological Evaluation of Pyrimidine Nucleosides Fused with 3',4'-Tetrahydrofuran Ring

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A number of 2',3'-deoxynucleosides have been discovered to possess significant antiviral activity against HIV-1 and other viruses. Since it has been suggested that proper conformation of the dideoxynucleosides in terms of ring puckering of the five-membered sugar moiety is required for them to exhibit antiviral activity, a number of nucleoside analogues to fix sugar-ring puckering have been synthesized and evaluated for antiviral activity. Among them, bicyclic nucleoside analogues like the 3',4'-oxetane-ring or 2',3'-methylene fused nucleosides have been reported to inhibit HIV replication, but 3',4'-cyclopentane fused pyrimidine nucleosides did not show antiviral activity. Therefore, based on these findings, novel 3',4'-tetrahydrofuran fused pyrimidine nucleosides were designed and synthesized to obtain further information regarding the correlation between sugar ring conformation and antiviral activity. The desired pyrimidine nucleosides and their 2'-deoxy anlogues were straightforwardly synthesized, starting from D-glucose. 3',4'-Tetrahydrofurn ring was introduced by the intramolecular cyclization reaction of 3-C-hydroxymethyl-4-bis-mesyl sugar derivative with sodium hydride. The final nucleosides were assayed for antiviral activities against HIV-1, VSV and HCMV, among which thymidine analogue and its corresponding 2'-deoxy analogue exhited high cytotoxicity instead of antiviral activities. It is concluded that this class of conformationally rigid nucleosides can be a lead for antitumor agents, not antiviral agents. Synthesis biological activity will be presented in the meeting.

[PD1-65] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis of 5-Azacytidine Nucleosides With Rigid Sugar Moiety As Potential Antitumor Agents

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Unmodified nucleosides exist in either S-type or N-type conformation, but due to the low energy barrier between this two dominating conformers a fast equilibrium between them exists in solution state. Therefore, many approaches to lock the puckering of the furanose ring in N-type or S-type have been made since HIV-1 reverse transcriptase is able to discriminate between two conformationally locked carbocyclic AZT triphosphate analogues. Recently, since we have found antitumor activity of 3',4'-tetrahydrofuran fused pyrimidine nucleosides locked into C1'-exo conformation, it was interesting to study the antitumor activity of the nucleosides locked into the S-the or N-type conformation. For this purpose, we synthesized the 5-azacytidine nucleoside analogues locked into the S-type or N-type conformation because 5-azacytidine derivatives like D-5-azacytidine and 2'-deoxy-D-5-azacytidine exhibited very potent anti-leukemic activity. The desired bicyclic 3'-O,5'-C-methylene-linked and 2'-O,5'-C-methylene-linked nucleosides were readily synthesized from D-glucose according to the modified Wengel's procedure and tested against several cancer cell lines. It was found that both analogues exhibited moderate anti-leukemic activity, but they did not show significant antitumor activity against lung cancer and colon cancer cells, indicating that conformationally locked nucleosides can be a good lead for the development of anticancer, not antiviral agents. Synthesis and biological activity will be presented in the meeting.

[PD1-66] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

DESIGN AND SYNTHESIS OF A3 ADENOSINE RECEPTOR LIGANDS, 3'-FLUORO ANALOGUES OF Cl-IB-MECA

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2-Chloro-N6-(3-iodobenzyl)-adenosine-5'-methylcarboxamide (2-Cl-IB-MECA) has been recognized to be one of the most selective agonists (Ki = 1.0 nM) for rat adenosine A3 receptor. On the basis of the high binding affinity of 2-Cl-IB-MECA to adenosine A3 receptor, it was interesting to find out whether 2'- and/or 3'-hydroxyl group of 2-Cl-IB-MECA is essential for the binding affinity to the receptor. Thus, we synthesized the new ligands, 2'-fluoro analogues of 2-Cl-IB-MECA to substitute the 2'-hydroxyl group of 2-Cl-IB-MECA with fluorine and evaluated them for binding affinity to adenosine A3 receptor, in which significant decrease of the binding affinity was observed, indicating 2'-hydroxyl group is essential for binding affinity. Based on this finding, it was interesting to synthesize the corresponding 3'-fluoro analogues of 2-Cl-IB-MECA and evaluated them for binding affinity to adenosine A3 receptor. In order to synthesize 3'-fluoro analogues of 2-Cl-IB-MECA, the glycosyl donor, D-3-deoxy-3-fluororibosyl acetate was first synthesized via the regioselective opening of 2,3-epoxide with fluoride anion, starting from D-xylose, condensed with silylated 2,6-dichloropurine, and then converted to the final nucleosides. The synthesized nucleosides were assayed for binding affinity to adenosine A3 receptor, in which significant correlation between 3'-hydroxyl group and 3'-fluorine atom was observed. Synthesis and binding affinity to adenosine A3 receptor will be presented in the meeting.

[PD1-67] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Asymmetric Synthesis of 12(S)-HETE

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(*S*) and (*R*) 12-HETE, endogenous eicosanoids, have recently been discovered to be implicated in a number of important biological activities. In particular, it has recently been reported by us that both the capsaicin-activated channel of sensory neurons and the cloned capsaicin receptor (VR1) are activated by the eicosanoids including these metabolites. We report herein a novel and efficient asymmetric synthesis of highly enantiomerically enriched 12(*S*)-HETE via enzymatic kinetic resolution of the key allylic alcohol synthon.

[PD1-68] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]