A dimeric Cinchona alkaloid ammonium salt, a,a'-bis[O(9)-allylcinchonidinium]-m-xylene dibromide, has been developed as a new efficient phase transfer catalyst; the catalytic enantioselective alkylation of N-(diphenylmethylene)glycine tert-butyl ester proceed in a high enantiomeric excess (90~99% ee).

[PD1-2] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Synrthesis and antiviral activity of 2'-UP-azido-2',3'-dideoxy-4'-thionucleosides

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Since the discovery of D-3'-azido-3'-deoxythymidine (AZT) as potent anti-AIDS drug, many D-2',3'-dideoxynucleosides with various substituents such as fluoro or azido group at C2 or C3 position have been synthesized and evaluated for antiviral activities. Among these compounds, D-2'-UP-azido-2',3'-dideoxynucleosides have exhibited very potent anti-HIV activity. Based on the bioisosteric rationale, we have been interested in synthesizing the corresponding D-2'-UP-azido-2',3'-dideoxy-4'-thionucleo-sides and comparing their antiviral activities. The target nucleosides were synthesized from the condensation of nucleoside bases with D-4-thiosugar acetate. Synthesis of 4-thiosugar acetate was started from L-xylose which was converted to the 4-thioarabitol derivative. The key step, azidation was completed by mesylation of the alcohol followed by treating with sodium azide. Azidation was proceeded with retention of stereochemistry unlike DAST fluorination. Finally synthesis of sugar acetate was accomplished by oxidation to the sulfoxide followed by Pummerer rearrangement. Using this sugar acetate, we have obtaineded variuous pyrimidine and purine nucleosides and evaluated them for antiviral activities. Most of the synthesized compounds were found to be slightly active but they were cytotoxic, too. So, antiviral activities were originated from inherent cytotoxicity of the synthesized compounds.

[PD1-3] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Synthesis of Sweet Sesquiterpene, (+)-Hernandulcin

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(+)-Hernandulcin was isolated as a sweet bisabolane sesquiterpene constituent of an aztec herb Lippia dulcis Trev. (Verbenaceae). It has shown to be 1,000 times as sweet as sucrose and non-toxic to human. The absolute stereochemistry of (+)-hernandulcin was determined by Mori et al., in 1985 by means of synthesizing all of the four possible stereoisomers. A concise synthesis of (+)-hernandulcin from (-)-isopulegol is reported here. Selective epoxidation followed by opening of the epoxide with prenyl Grignard, which was prepared from prenyl chloride and magnesium in the presence of purified cuprous iodide, afforded the tertiary alcohol with correct stereochemistry. Oxidation of the secondary alcohol and double bond formation provided (+)-hernandulcin.

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

Synthesis and Biological Activity of FTase Inhibitors Containing Isoleucyl Surrogates

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Oncogenic mutations of ras genes have been found in 30% of all human cancers including 50% of colon cancer, 90% of pancreas cancer, 50% of lung cancer and thyroid gland cancers. The transformed ras proteins, e.g., H-Ras, N-Ras, K-RasA, K-RasB etc., translated by the mutated ras genes result in the unregulated cell growth, thereby causing cell tumorization. This reaction is catalyzed by the enzyme, farnesyltransferase (FTase). Therefore, inhibitors of FTase should serve to block cell transforming activity by inhibiting the action of the mutated ras gene. Therefore, FTase has been focused as a new target for development of anticancer agents. Based on the N-terminal CAAX box of ras proteins, many types of peptidomimetic FTase inhibitors have been reported.
The synthesis and the biological activity of non-peptide FTase inhibitors will be discussed in this presentation. Cysteine of the CAAX box have been replaced with imidazole substituent and isoleucyl moiety replaced with a various alkyl, cycloalkyl surrogates. Evaluation of biological activity was carried out with purified FTase and MTT based cell growth inhibition. Many FTase inhibitors showed strong inhibition against K-ras farnesylation as well as ras-transformed cell growth without showing cytotoxicity in wild type cell line, NIH3T3.
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[PD1-5] [04/20/2001 (Fri) 13:30 - 14:30 / Hall 4]

Syntheses of Certain 3-Aryl-2-propenoates and Evaluation of their Cytotoxicity

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In our search for novel antitumor agents from natural sources, we isolated a phenyl propanoid, methyl 3,4-dihydroxycinnamate (methyl caffeate 4a), from the plant Notopterygium incisum. This compound showed a significant cytotoxicity against various cancer cell lines and greatly inhibited the invasion of B16 melanoma cells. Structurally, 4a possesses an alpha,beta-unsaturated carbonyl, which can be considered as a Michael acceptor, an active moiety often employed in the design of anticancer drugs. In addition, a number of alpha,beta-unsaturated ketones have demonstrated preferential activity toward thiol. Alkylation with a cellular thiol such as glutathione (GSH) may also occur with cinnamates like 4a, leading to adducts at beta-position. Hence, alpha,beta-unsaturated carbonyl-containing compounds may be free from problems of mutagenicity and carcinogenicity that are associated with many alkylating agents used in cancer chemotherapy. Taking into consideration this structural feature and the interesting bioactivity of the compound 4a, the present investigation aims at preparing a number of 4a analogues and related 3-aryl-2-propenoates in order to evaluate their cytotoxicity. Caffeates (4a ~ 4c) were obtained by refluxing caffeic acid in excess alcohol used as solvent in the presence of a catalytic amount of HCl . Other cinnamates (4d ~ 4m) were synthesized in good yields by a Wittig reaction. The two caffeamides 3a, 3b were synthesized through a sequence: protection of the phenol groups with methoxycarbonyls, coupling of the protected caffeic acid with hydroxyamine or aniline and deprotection by sodium methoxide. Reduction of the double bond of the propenoate 4d was carried out using hydrogen (1 atm) and Pd/C (10%) to afford the dihydrocinnamate 5 in a quantitative yield. E)-3-[2-(1,4-Dihydroxy-9,10-dione)anthracenyl]- and (E)-3-[2-(1,4-dihydroxy-5,8-dione)naphthalenyl]-2-propenoates were synthesized from 2-formyl-1,4-9,10-tetramethoxyanthracene(6a) and 2-formyl-1,4,9,10-tetramethoxynaphthalene(6b). The synthesized compounds were evaluated for their cytotoxicities. It was found that methyl and ethyl 2,5-dihydroxycinnamates displayed a potent cytotoxicity against a variety of cancer cell lines. The simple analogues (E)-methyl/ethyl 3-[2-(1,4-dihydroxy-9,10-dione)anthracenyl]-2-propenoates exerted an