Several studies of terbenzimidazoles and bibenzimidazoles suggested that benzimidazoles, especially 5-nitro-2-(para-methoxyphenyl)benzimidazole, possess topoisomerase I inhibition activities. In order to find out the structure activity relationship of 5-nitro-2-phenyl-benzimidazoles, eight derivatives that are substituted at the para position of 2-phenyl moiety were selected, synthesized & evaluated considering their electronic or lipophilic parameters. Both the topoisomerase I inhibiton activities and the cytotoxicities were related neither to the electronic nor lipophilic parameters. These data suggest that their activities may be related to other parameters including steric bulk or hydrogen-bonding capacities. Further studies are on the way to investigate this relationship.

[PD1-13] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Asymmetric synthesis of (2S, 3R, 4E) 5-Aryl-4-pentene-1,3-diol-2-aminoueras

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(2S 3R, 4E) 5-Aryl-4-pentene-1,3-diol-2-aminoueras had been synthesized for their cytotoxic activity. Pinene was oxidized with KMnO4 to give 2-hydroxy-3-pinanone, which treated with ethyl glycinate to yield iminoglycinate and then reacted with aldehyde derivatives and titanium enolate to afford 3-hydroxy aldol compounds. These aldol compounds was hydrolyzed with HCl and reduced with NaBH4 to give 2-amino-1,3-diols, which was treated with alkyl isocyanates to yield 5-aryl-4-pentene-1,3-diol-2-aminoueras. The aldehyde derivatives was synthesized in three steps from benzelaldehydes.

[PD1-14] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Synthesis of N-methylspiro[1,2,3,4-tetrahydro-naphthalene-1,2'-pyrrolidine]

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A pathway for synthesis of N-methylspiro[1,2,3,4-tetrahydro-naphthalene-1,2'- pyrrolidine] was developed. Formation of the imine compound from α-tetralone and methylamine using titanium tetrachloride followed by ddition of allylmagnesium bromide gave (1-allyl-1,2,3,4-tetrahydro-naphthalen-1-yl)methylamine. Protection of (1-allyl- 1,2,3,4- tetrahydro-naphthalen-1-yl)methylamine followed by substitution reaction with di-tert-butyl carbonate in 10% sodium hydroxide solution gave (1-allyl-1,2,3,4- tetrahydro- thalen-1-yl)methylcarbamic acid tert-butyl ester. Hydroboration-oxidation of (1-allyl-1,2,3,4-tetrahydro-naphthalen-1-yl) methylcarbamic acid tert-butyl ester with borane disulfide complex or borane-THF complex gave [1-(3-hydroxyypropyl-1,2,3,4- tetrahydro-naphthalen-1-yl)methylcarbamic acid tert- butyl ester and deprotection of t-Boc group in 6N hydrochloric acid solution gave 3-(1-methylamino-1,2,3,4-tetrahydro- naphthalen-1-yl)-propan-1-ol. Finally, cyclization of the amino compound in Mitsunobu conditions provided N-methylspiro[1,2,3,4-tetrahydro-naphthalene-1,2'-pyrrolidine].

[PD1-15] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

The Synthesis of Novel Cyclobutyl Nucleoside as Potential Antiviral Agents

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Carbonucleosides has extensively been studied as a promising anti-viral agents having chemical and metabolical stability. As yet there are no rules relating the structures of carbocyclic nucleosides to their therapeutic activity, although trends among certain kinds of structure have been tentatively put forward. In our research program for discovery of anti-viral drugs, the novel cyclobutyl nucleosides can be expected to be potential antiviral drugs as analogues of cyclobut-A, anti-HBV agent. The key cyclobutyl intermediate synthesized by ring contraction reaction using zirconium complex, was condensed with purine base for synthesis of the novel carbocyclic nucleosides.

[PD1-16] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Syntheses of Aminoalcohols with Alkenyl Substituents for the Development of Tissue Factor Inhibitors and Their in vitro Nanomolar Level-Activities

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Tissue Factor (TF), a principal initiator of the veterbrate coagulation cascade is known to to induced in endothelial cells, monocytes and macrophages by inflammetry stimuli and in many pathological conditions. Through our synthetic efforts to develop new TF inhibitors, seventeen N-C-18 alkenyl group (9-octadecenyl or 9,12-octadecadienyl) substituted aminoalcohols (2-aminoethanol, 1-amino-2-propanol and 3-amino-1-propanol) were prepared and their in vitro TF inhibitory activities were examined. Except one case, they all exhibit nanomolar level activities (1.1~7.7×10^-9 mole/TF unit). Details of the studies will be discussed.

[PD1-17] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Synthesis and Biological Activity of 1β-Methyl-2-[5-(2-N-Substituted aminoethylcarbamoyl)pyrrolidin-3-ylthio]carbapenem Derivatives.

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The synthesis of a new series of 1β-methylcarbapenems having the substituted aminoethyl-carbamoylpyrrolidine moiety is described. Their in vitro antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of substituent on the pyrrolidine ring was investigated. In particular, the compound 11g having piperazinyl urea moiety showed the most potent antibacterial activity.

[PD1-18] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Stereoselective synthesis of carbocyclic analogue of Nucleocidin