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A convenient pathway for synthesis of trans-metanicotine analogues was developed. trans-Metanicotine, a subtype(alpha4beta2)-selective ligand for neuronal nicotinic acetylcholine receptor, is under clinical phase for Alzheimer's disease. Allylation of N-methyl aldimines with allylmagnesium bromide yielded methyl-(1-aryl-but-3-enyl)amines. Protection of the amines with Boc group and followed by Heck reaction with 3-bromopyridine gave methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl) carbamic acid tert-butyl esters. Following deprotection of N-Boc group provided methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)amines in good yields. Thus, trans-metanicotine analogues modified at the α-position of the methylamino group with various aryl groups can be obtained in 5 steps.

[PD1-11] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis of Novel TNF-α Production Inhibitors. 2-[3-(Cyclopentyloxy)-4-methoxyphenyl]-substituted-1-isoindolinone derivatives

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This study describes the synthesis and in vitro evaluation of 2-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-isoindolinone derivatives substituted on benzene moiety of isoindoline ring for the inhibition of TNF-α production. From this study, we have found the 6-C position on isoindolinone ring is an optimal derivatization site. Among the compounds synthesized, 6-amino-2-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-isoindolinone (6) was the most potent in inhibitory activity of TNF-α production in LPS-stimulated RAW264.7 cells.

[PD1-12] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis of Chelerythrine, Natural Benzo[c]phenanthridine Alkaloid

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Benzo[c]phenanthridines are naturally occurring alkaloids which have demonstrated numerous biological activities. Among these structures, fagaridine, nitidine and fagaronine have solicited much attention as antitumor drugs. Many synthetic approaches to benzo[c]phenanthridine alkaloids leading to natural products have been reported, but relatively few studies of synthetic analogues have been described. These alkaloids have also demonstrated binding affinities to DNA, have been presumed to be intercalators and have been shown to be inhibitors of DNA topoisomerase I and II, the well known targets for clinically important and emerging antitumor drugs.
As part of our endeavor to develop potential antitumor agents, we have tried to synthesize benzo[c] phenanthridine alkaloids. Our strategy is based on the synthesis of substituted 3-arylisoquinolines which is a crucial intermediates for the formation of C ring of these alkaloids. The synthesis of chelerythrine and other derivatives will be described.

[PD1-13] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Pimarane Cyclooxygenase 2 (COX-2) Inhibitor and its Structure-Activity Relationship

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Recently, we have reported the isolation of a novel pimarane diterpene, acanthoic acid, from the Korean medicinal plant which has been traditionally used for treating rheumatism. In particular, acanthoic acid turned out to be biologically attractive because it has been showned to exhibit an excellent suppression of interleukin-1(IL-1) and tumor necrosis factor-α(TNF-α) at low level which are major proinflammatory cytokines.
More recently, the COX-2 inhibitory activities of acanthoic acid have also been investigated by us as an extension of the stuies on its anti-inflammatory effects as well as therapeutic utilities.
We herein report acanthoic acid and its analogues as a novel COX-2 inhibitor as well as structure-activity relationship of acanthoic acid.
In addition, the interaction mode of acanthoic acid with the COX-2 active site and antiinflammatory effects of the highly bioactivity-enhanced acanthoic acid analogues will be presented.

[PD1-14] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Asymmetric Synthesis of (1R, 2S)-1-Allyl-2-Silanyloxy Carbamates using CSI reaction

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A plethora of pharmaceutically and biologically valuable compounds comparise 1, 2-amino hydroxy functional groups. The substances are usually involved in exhibiting a variety of biological activities. The representatives are the glycosidase inhibitors (-)-swainsonine, (+)-castanoper-mine and azasugars, and (-)-statine as the key constituent of the aspartic protease inhibitor pepstatin. In addition, others include the neurotrophic agent (+)-lactacystin, the antibiotic (-)-furanomycin, the antifungal agent (-)-anisomycin and so forth.
We have recently described synthetic method for N-protected allylic amines from allyl ethers using chlorosulfonyl isocyanate(CSI) via the stable allylic carbocation.
In this presentation, we will report asymmetric synthetic method for (1R, 2S)-1-allyl-2-silanyloxy carbamates (1, 2-amino alcohol) by the simple CSI reaction which we developed with various allyl ethers and discuss mechanism of these reactions.

[PD1-15] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis of Ester Type Derivatives as Inhibitors of Acetylcholinesterase

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We have known that acetylcholinesterase inhibitiors are effective in enhancing cholinergic activity and useful in improving the memory of Alzheimer's patients. By structure-activity relationship studies and structural analysis, we have focused on the discovery of potent inhibitors of acetylcholinesterase and synthesized a series of 4-[4-(benzhydryloxy)piperidino]butyl benzoate's derivatives from reaction 4-[4-(benzhydryloxy)piperidino]-1-butanol with some para substituted benzoic acid by 1-ehtyl-3-(3-dimethylaminopropyl)carbodiimide and 4-dimethylaminopyridine coupling. Also,4-[4-(benzhydryloxy)-