[PD1-19] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Synthesis of Novel 3'-Deoxy-3'-C-hydroxymethyl Nucleosides with Conformationally Rigid Sugar Moiety as Potential Antiviral Agents

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Oxetanocin A is a naturally occurring nucleoside which shows potent anti-Hiv activity. The ring expanded 3'-C-hydroxymethyl analogue of oxetanocin A also exhibited similar antiviral activity, but its carbocyclic analogue was totally devoid of antiviral activity. This difference in antiviral activity might be due to absolutely different sugar conformation. Since antiviral activity of the ring expanded analogue was reported to due to the superposition of its 3'-C-hydroxymethyl group and hydroxymethyl substituent of oxetanocin A, we synthesized conformationally rigid 3'-C-hydroxymethyl derivative in which 2'-hydroxyl group is linked to the 4'-position. The preliminary result indicates that its 3'-hydroxyl group superimposed well with that of ring expanded 3'-C-hydroxymethyl analogue. We also synthesized another conformationally rigid 3'-C-hydroxymethyl derivative in which 2'-hydroxyl group is connected to the 6'-position. These compounds fix the orientations of 3'- and 5'-hydroxymethyl groups which will affect the affinity to kinases and finally antiviral activity. Synthesis and antiviral activities will be in detail presented in the meeting.

[PD1-20] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

New approach to the synthesis of α-amino acids by CSI reaction with allyl ethers

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The high level of interest in α-amino acids stems from their biological stability, their utility in studies of enzyme mechanisms, and their use as enzyme inhibitors. Furthermore, once incorporated into peptides, these amino acids influence the conformation of the protein, thereby altering its properties. In recent years, much attention has been paid to the development of concise and flexible synthetic approaches to α-amino acids, allowing facile incorporation of functional groups and structural variability.
Nowadays, we developed synthetic method for N-protected allylic amines from allyl ethers using chlorosulfonyl isocyanate(CSI) via the stable allylic carbocation. In this presentation, the method for the synthesis of various α-amino acids from allyl ethers through the use of CSI reaction will be described. First, allyl ethers were converted to the corresponding N-allylcarbarmates by CSI reaction and then double bond of allyl group was oxidized to form of α-amino acids
As one of our results, N-Cbz methylphenylalanate was obtained from 1,4-diphenylbut-2-enyl benzyl ether via benzyl(1-benzyl-3-phenylallyl)carbarmate as an intermediate.

[PD1-21] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Synthesis of 2-(4-Methoxyphenyl)-pyrrolo[2,1-d]pyrido[3,4-b][1,5]thiazepine

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Calcium channel blockers have been proven to be clinically useful agents in treating various cardiovascular disorders. The chemical structures of the major blockes are classified into three groups, dihydropyridines, phenylalkylamines and 1,5-benzothiazepines, which are represented by nifedipine, verapamil and diltiazem, respectively. Because of their highly clinical usefulness a number of modifications have been done on dihydropyridines and phenylalkylamines for the purpose improving their bioavailability and duration of action. However, there have been only a few reports concerning modifications of benzothiazepines. Diltiazem is usually administered twice or three times a day and its antihypertensive potency is far less than that of dihydropyridines. In order to synthesize a potent and long-lasting diltiazem congener, we intended to synthesize the hybrid structure of nifedipine and 8-chlorodiltiazem. 4-(1-pyrrolyl)amino-3-mercaptopyridine was synthesize from 4-amino-3-mercaptopyridine and 2,5-dimethoxytetrahydrofuran, and it was reacted with ethyl 2-(4-methoxyphenyl)-2-bromoacetate to give 2-(4-methoxy phenyl)-pyrrolo[2,1-d]-pyrido[3,4-b][1,5]thiazepine derivatives.

[PD1-22] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Asymmetric synthesis of (R)-(+)-etomoxir via enzymatic resolution

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An asymmetric synthesis of (R)-(+)-etomoxir 1, employing enzymatic resolution of ethyl 2-alkyl-2,3-dihydroxypropionate using Amano AK via transacylation is reported. Highly enantioselective enzymatic resolution of ethyl 2-alkyl-2,3-dihydroxypropionate was developed by using Amano AK in MTBE. By this process, (R)-(+)-etomoxir could be prepared in 30% yield and 98% ee over five steps from triehyl phosphonoacetate.

[PD1-23] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Comparative Molecular Field Analysis (CoMFA) Study of Antitumor 3 - Arylisoquinolines

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A three-dimensional quantitative structure-activity relationship (3D-QSAR) was performed for antitumor 3-arylisoquinoline derivatives by using comparative molecular field analysis (CoMFA) against four tumor cell-lines (A549, SK-OV-3, SK-MEL-2, and HCT15). CoMFA procedure was progressed with a set of 83 3-arylisoquinolines and x-ray crystal structure of 7,8-dimethoxy-3-(2-methylphenyl)isoquinolinone was used to determine molecular conformations. As a result we could get good Cross-Validated R^2 (Q^2) values and pharmacophore models. The synthesis and CoMFA of antitumor 3-arylisoquinoline will be discussed.

[PD1-24] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]