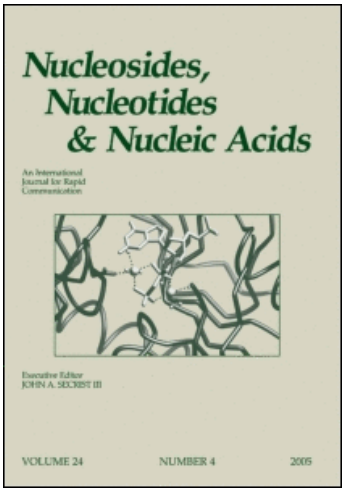

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Enantioselective Synthesis of Carbocyclic Nucleosides by Enzymatic Approach and the Anticancer Activities

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ENANTIOSELECTIVE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES BY ENZYMATIC APPROACH AND THE ANTICANCER ACTIVITIES

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Summary: Enantioselective synthesis of carbocyclic nucleosides, aristeromycin, neplanomycin A and their homologues has been completed by a combination of enzymatic and non-enzymatic procedures starting with a bicyclic meso-diester **2**. The study on anticancer activities of them showed that the cytosine homologue exhibits most remarkable activity against L1210 leukemia in mice.

Introduction Asymmetric synthesis has come to the forefront of modern organic synthesis. The efficient creation of new chiral synthons with desired asymmetric centers and functional groups may be most ideal if it is carried out in a catalytic manner. Our synthetic strategy for obtaining various nucleosides has been designed by the following principle.

(1) Symmetrization: retrosyntheses of most of complex natural products can be designed in such a way to start with symmetric and simplified diesters having σ-symmetry in the prochiral or meso form as schematized in SCHEME 1.

(2) Asymmetrization: the symmetric diesters are then subjected to asymmetric hydrolysis with pig liver esterase (PLE) to create the corresponding chiral half-esters. (enzymatic conversion of σ-symmetry-substrates to C_1-symmetry-intermediates)

(3) The chiral half-esters are converted to key intermediates not only for the target molecules but also for the related molecules (structure-activity-relationships) by non-enzymatic procedures.

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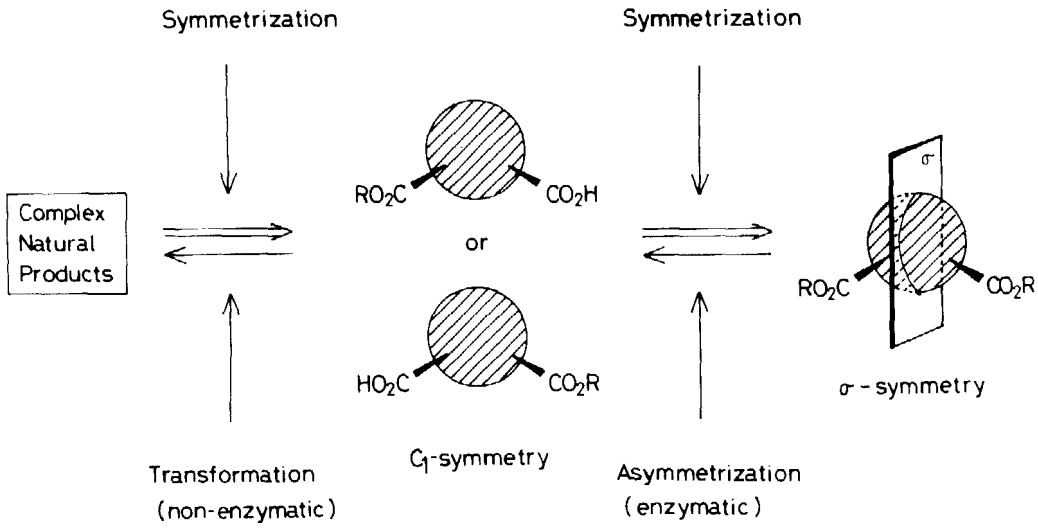
SCHEME 1

Retrosynthesis of Natural Products based on Symmetrization-asymmetrization Concept

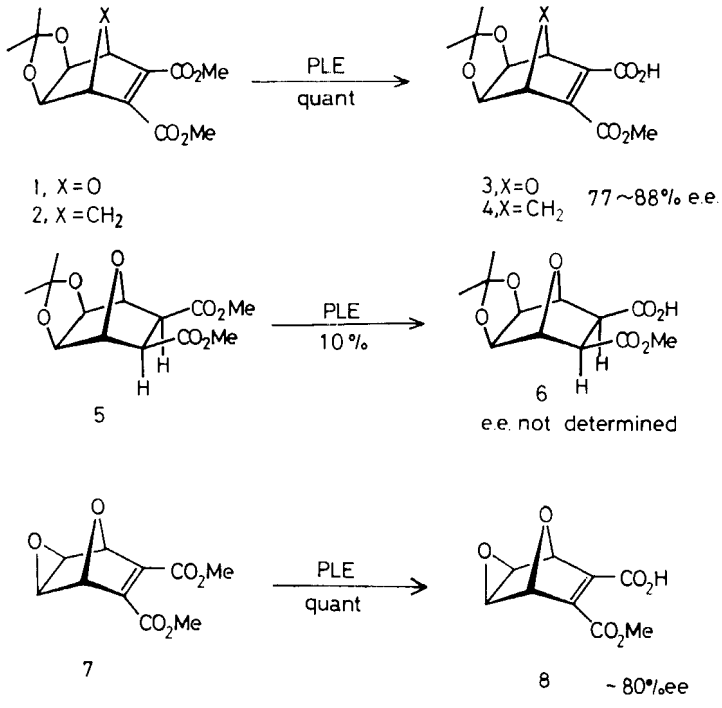


Enantioselective synthesis of C- and N-nucleosides, showdomycin, 6-azapseudouridine and cordycepin[1,2,3] Although the study of the asymmetric synthesis of natural products has been considerably intensified in recent years, no successful methodology is available in the nucleoside field. As an extension of our enzymatic approach to natural product synthesis, sugar moieties of various nucleosides were considered to be a good target for demonstrating our concept. Two symmetrically constituted diesters, **1** and **5**, were selected as the substrates for the asymmetric hydrolysis by esterases, although such bicyclic and rather rigid meso compounds had not yet been subjected to an enzyme-mediated reaction. The substrates, **1** and **5**, both easily available from a Diels-Alder reaction, were subjected to the enzyme reaction, separately (SCHEME 2).

A preliminary study showed that the rate of hydrolysis by PLE superior to that by α-chymotrypsin. It was gratifying to find that the unsaturated diester **1** was more efficiently hydrolyzed than the saturated

SCHEME 2

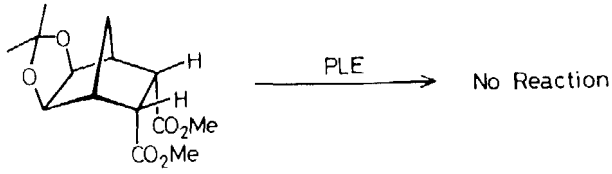
Asymmetric Hydrolysis of Bicyclic diesters with Pig Liver Esterase



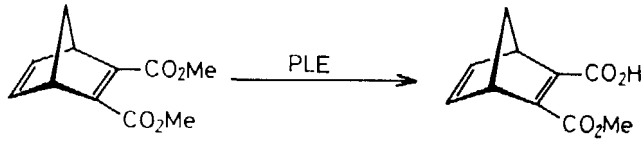
diester **5**. In a typical experiment, **1** (3g) in 0.1M phosphate buffer (300ml, pH 8.0) and acetone (30ml) were incubated with PLE (4140units) at 32°C for 4hr, and optically active half-ester **3** was thus obtained in 96% chemical yield and about 80%ee after usual work-up. On the other hand, a symmetric epoxy diester **7** was also considered to be a good substrate for the synthesis of another nucleoside, cordycepin, which belongs to the family of N-nucleosides with a 3-deoxyribose moiety. The substrate **7** was treated with PLE to yield the expected chiral half-ester **8** in an excellent chemical yield and about 80%ee. The absolute structures and optical purity of the half-esters were determined by conversion to the known natural products. The half-ester **3** and **8** described above were transformed to methyl L- and D-ribosides, (+)-showdomycin, (-)-6-azapseudouridine, and (-)-cordycepin, as summarized in SCHEME 7. It should be mentioned here that a symmetric

SCHEME 3

Asymmetric Hydrolysis of Bicyclic diesters with Pig Liver Esterase



9



10 11

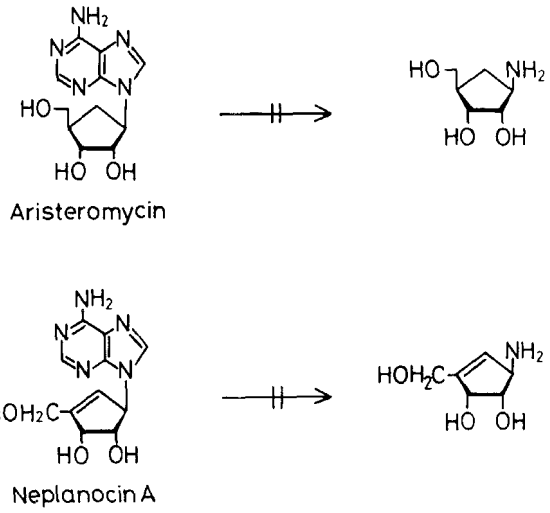
41%e.e.

diester **9** with the endo configuration was completely inert to PLE and the unsaturated diester **10** was hydrolyzed with PLE to give **11** in a low optical yield (SCHEME 3).

Enantioselective synthesis of carbocyclic nucleosides, (-)-aristeromycin, (-)-neplanocin A, and the homologues[4,5,6]

A new carbocyclic antibiotic named neplanocin A was isolated from Actinoplanacea ampullariella in 1980 and it has been shown that neplanocin A is a novel carbocyclic analogue of adenosine with a cyclopentene moiety and that it exhibits remarkable antitumor activity against L1210 leukemia in mice.[7,8,9] We became interested in the synthesis of neplanocin A and the homologues in optically active form, because no one succeeded even in the enantioselective synthesis of aristeromycin isolated from a microorganism in 1968. The chiral carbocyclic moiety seems to be not easily accessible by conventional

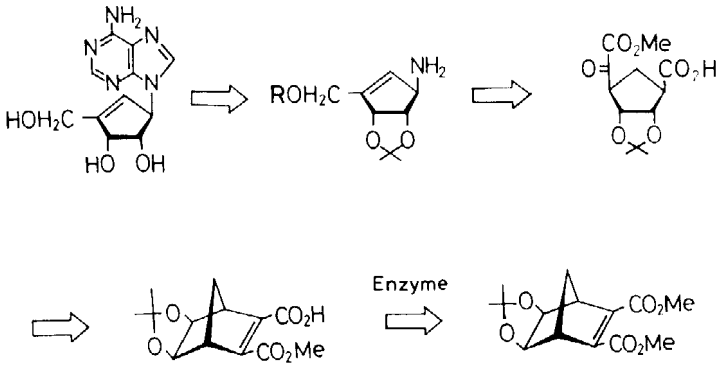
SCHEME 4



synthetic means or by the partial degradation of aristeromycin or neplanocin (SCHEME 4). As shown in the synthetic strategy (SCHEME 5) based on symmetrization-asymmetrization concept, an efficient access to the chiral cyclopentane derivatives was considered to be the enantioselective generation of an asymmetric half-ester **4** from a meso diester **2**. Thus, the meso-diester **2** efficiently prepared from cyclopentadiene and dimethyl acethylenedicarboxylate was treated with pig liver esterase in aqueous acetone to afford the half-ester **4** in quantitative chemical yield. The optical purity of the half-ester **4** was found to be about 80-88%ee, but the optically pure material was most easily and preferably obtained by recrystallization of the δ-lactone **14**. Ozonolysis of **4** in ethyl acetate at 78°C for 3 h afforded α-ketoester **12** having the desired sugar-skeleton. Crystalline δ-lactone **14** showed $[\alpha]_D^{25}$+44,4° after recrystallization from a mixed solvent of methylene chloride, n-hexane and ether (1:5:5). As shown in SCHEME 6, the δ-lactone **14** was converted not only to neplanosin A but also to the various homologues (**15** → **16** → **17** → **18**). The biological activities of them are shown in TABLE 1 and it is interesting to note that the cytosine homologue exhibits most remarkable antitumor activity. The enzymatic approach to the new chiral synthons developed here has opened up a new avenue to natural carbocyclic nucleosides and also to various unnatural homologues (SCHEME 7).

SCHEME 5

Synthetic Strategy for (-)Neplanocin A by Chemicoenzymatic Approach



SCHEME 6

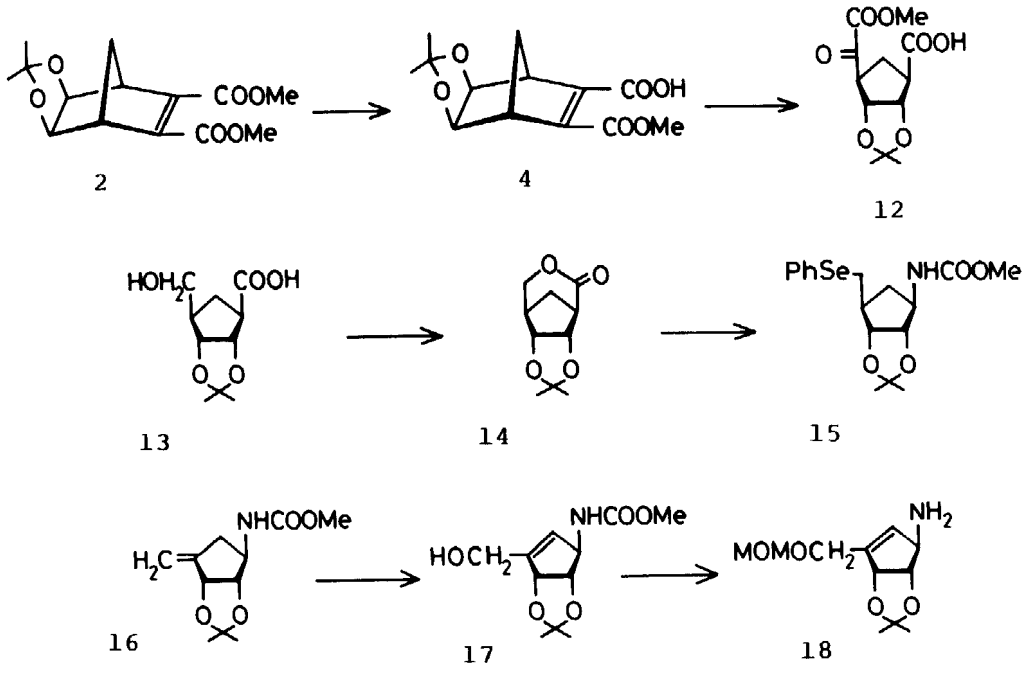
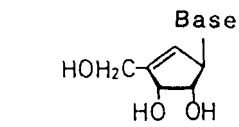
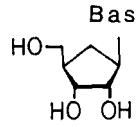


TABLE 1

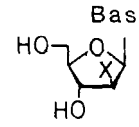
Biological Activities of Aristeromycin and Neplanocin A Analogs



Base: Uracil (1)
Cytosine (2)
AICA (3)
Guanine (4)
Adenine (6)
(Neplanocin A)



Base: AICA (5)
Adenine (7)
(Aristeromycin)
Cytosine (8)
(Carbodine)



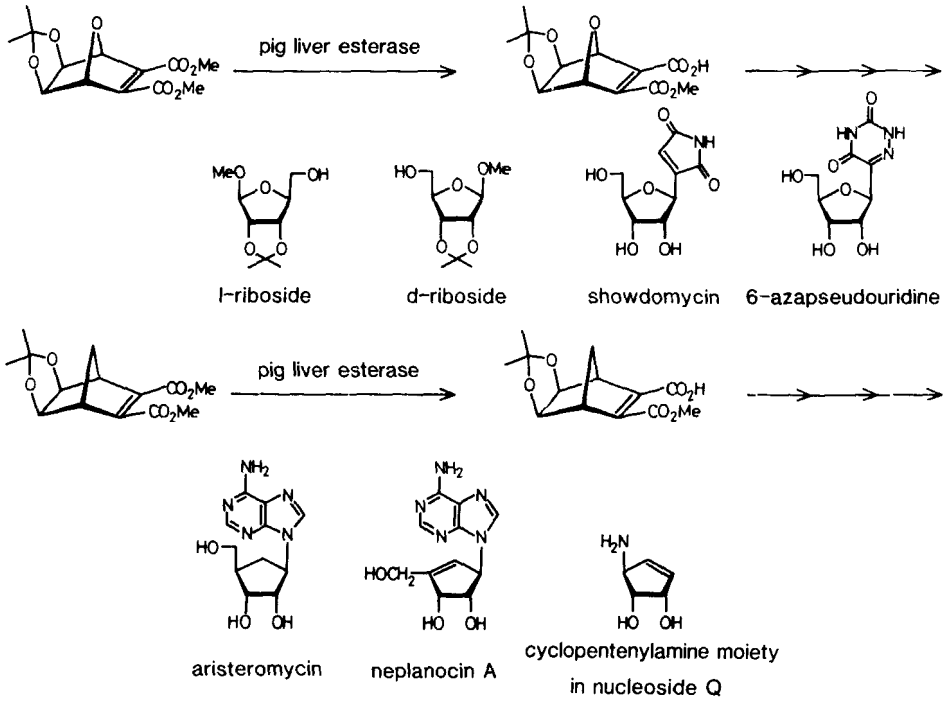
Base: 5-FU X:H (9)
Cytosine X:OH (10)

	1	2	3	4	5	6	7	8	9	10
Cytotoxic Con.(μg/ml)•	>100	<0.3	43	4.4	8.6	<0.3	<0.3	6.5	<1	<1
ILS % (mg/kg,day)••		77 (1)				38 (1)	2 (100)	50 (150)	55 (80)	133 (20)

• KB cells in culture (in vitro)

•• L1210 leukemia in mice (in vivo) (ip-ip)

SCHEME 7 Chemicoenzymatic Approach to Nucleosides



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