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SYNTHETIC STUDIES ON BIOLOGICALLY ACTIVE NATURAL PRODUCTS BY A CHEMICOENZYMATIC APPROACH

ENANTIOSELECTIVE SYNTHESIS OF C- AND N-NUCLEOSIDES, SHOWDOMYCIN, 6-AZAPSEUDOURIDINE AND CORDYCEPIN

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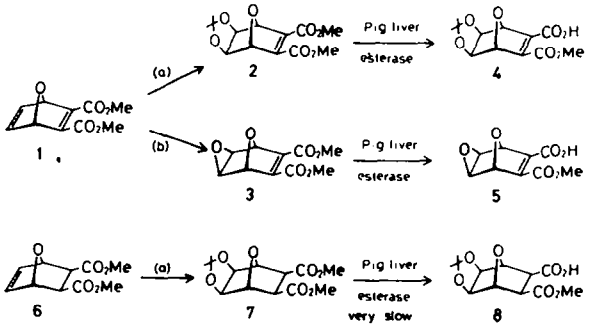
Abstract—An efficient synthesis of C- and N-nucleosides has been developed in an enantioselective and stereocontrolled manner starting from Diels–Alder adduct of furan and dimethyl acetylenedicarboxylate by chemicoenzymatic strategy. The symmetric unsaturated dimethyl esters **2** and **3** were almost quantitatively hydrolysed with pig liver esterase to yield half-esters **4** and **5** with reasonably high optical yields. Decarboxylative ozonolysis of the chiral half-esters **4** followed by chemical transformation afforded methyl L-riboside **12**, but after the enantiomer conversion (**4** to **13** and **5** to **28**) the methyl D-riboside (**17**), (+)-showdomycin (**22**), and (−)-6-azapseudouridine (**27**), were obtained from **13**, and (−)-cordycepin (**32**) was obtained from **28**.

Since the discovery of pseudouridine in 1957,[1] a number of naturally occurring C-nucleosides have been reported and attracted a great deal of synthetic study of their unique structures of C-glycosylated heterocycles and the interesting biological properties such as antibiotic, antiviral and antitumor activity.[2,3] Most of the synthetic approaches have been based on the utilization of natural carbohydrate precursors.[2b,3] Recent progress of the synthetic approaches to the sugar moiety of nucleosides starting from non-carbohydrate synthons or readily available meso compounds is noteworthy in the stereocontrolled manner.[4] However, they require a conventional optical resolution step, and recycling of the undesired enantiomer is required in a chirally economic synthesis.[5] Although the study of the asymmetric synthesis of natural products has considerably intensified in recent years, no successful methodology is available in the nucleoside field. We have recently initiated a program to investigate a useful combination of enzymatic and chemical procedures for the synthesis of biologically important and optically active natural products.[6] Until recently, the synthetically oriented information available on such enzyme-systems has been too limited to make the routine use of the methods attractive to organic chemists.[7] We wish to report here an efficient enantioselective synthesis of methyl L- and D-ribosides, (+)-showdomycin, (−)-6-azapseudouridine, and (−)-cordycepin by the chemicoenzymatic strategy.[6a]

Enzymatic process (*Scheme* 1)

Two symmetrically constituted diesters **2** and **7** were selected as the substrates for the asymmetric hydrolysis by esterase, although such bicyclic and rather rigid meso compounds have never been subjected to an enzyme-mediated reaction. Cohen's pioneering study on the active site and specificity of α-chymotrypsin disclosed basic information and structural requirements involved in the hydrolysis of acyclic and 6-membered cyclic substrates,[8] and Cohen *et al.* showed that diethyl fumarate is easily hydrolyzed by α-chymotrypsin to afford monoethyl fumarate in high yield. However, diethyl maleate is



Scheme 1. Enzymatic step.

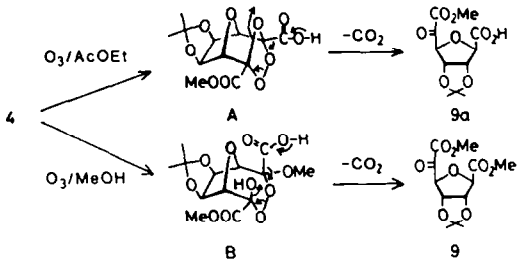
completely inert, and the reactivity of diethyl succinate is a little smaller than that of diethyl fumarate.[9] Our substrates **2** and **7** contain maleate and succinate moieties, respectively, suggesting that α-chymotrypsin is an inapplicable enzyme for our substrates. Actually, the rate of hydrolysis of **2** by α-chymotrypsin was found to be extremely slow and a large amount of the enzyme seemed necessary for synthetic purposes. Therefore, readily available pig liver esterase[10] was used, since it was originally employed in the case of β-hydroxy-β-methyl dimethyl glutarate by Sih *et al.*[11] A preliminary study showed that the rate of hydrolysis by pig liver esterase was found generally superior to that by α-chymotrypsin and the rate was roughly estimated in the decreasing order; dimethyl glutarate ≃ dimethyl succinate > dimethyl fumarate ≫ dimethyl maleate. Encouraged by this finding, symmetric diesters **2**[12] and **7**[13] both easily available from Diels–Alder reactions were subjected to the enzyme reaction, separately.

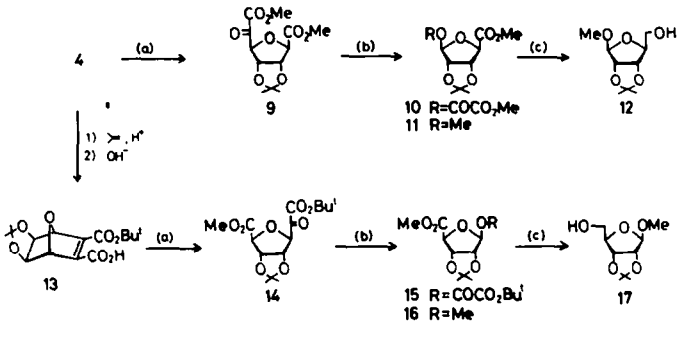
It was gratifying to find that the unsaturated diester **2** was, surprisingly, more efficiently hydrolysed than the saturated diester **7**. In a typical experiment, **2** (3 g) in 0.1 M phosphate buffer (300 mL, pH 8.0) and acetone (30 mL) was incubated with pig liver esterase (4140 units) at 32° for 4 hr, and optically active half-ester **4** was obtained in 96% yield after usual workup. The crude solid material showed $[\alpha]_D^{20} - 37°$ (*c* 1.0, $CHCl_3$) and it was recrystallized from CCl_4 and then twice from CCl_4-*n*-hexane, showing m.p. 115.5–117.5° and $[\alpha]_D^{20} - 49°$. The absolute configuration of **4** as well the optical purity of the crude half-ester **4** (about 77% ee) was determined by synthetic transformation to L-ribose derivative as described below. In the absence of the enzyme under the same reaction condition, the diester **2** was partially hydrolysed to afford racemic half-ester **4** in about 5% yield. Therefore, the optical yield of the enzymatic hydrolysis seems to be about 81% ee. The saturated diester was hydrolyzed very slowly to afford only 10% yield of optically active half-ester **8**[14] even after 24 hr incubation. Therefore, the access to the chiral sugar moieties of various nucleosides was extensively investigated from the unsaturated diester **4** and not from the saturated diester **8**. The epoxy half-ester **5** was also considered to be a chiral starting material for the synthesis of other nucleosides. Cordycepin,[15] which belongs to the family of N-nucleosides with 3-deoxyribose moiety was selected as a synthetic target. The symmetric epoxy diester **3**[16] was treated with pig liver esterase, as described in the hydrolysis of **2**, to yield **5**, m.p. 120–122°, $[\alpha]_D^{20} - 32°$ (*c* 0.50, $CHCl_3$) in quantitative yield. The results of the enzymatic step showed that pig liver esterase is more useful than α-chymotrypsin from a synthetic point of view, since the former has far wider substrate specificity.

Enantioselective synthesis of methyl L-*and* D-*ribosides* (*Scheme* 2)

Since no reliable specificity data are available in predicting the course and stereospecificity of enzymatic reactions for such rigid bicyclic systems, chemical transformations of **4** to known chiral compounds were first studied to determine the absolute configuration of **4** enzymatically generated. Thus, the half-ester **4** with $[\alpha]_D^{20} - 37°$ was directly subjected to ozonolysis in methanol at −78° for 15 min (100 mg scale). Anomalous ozonlysis with decarboxylative cleavage took place smoothly without any rearrangement,[17] and the desired product **9** was obtained as colorless oil in quantitative yield. This step is equally important as the enzymatic step, since the ozonolysis product **9** has ideally differentiated the two functional groups at the 1- and 4-positions. The α-keto ester **9** in racemic form was previously considered as a key intermediate for the synthesis of C-nucleosides by Just *et al.*, but obtained by multistep synthesis from a Diels–Alder adduct of furan and methyl nitroacrylate.[18] The decarboxylative ozonolysis in ethyl acetate afforded the free acid **9a** and can be reasonably explained by regiospecific decomposition of the ozonide intermediate A and B without any undesirable rearrangement and without losing the optical integrity.

Further Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid (MCPBA) had occurred with virtually complete selectivity to yield an oxalate derivative **10** in 77% yield from **4**. The crude solid material showed $[\alpha]_D^{22} + 59.8°$ (*c* 1.0, $CHCl_3$) and m.p.



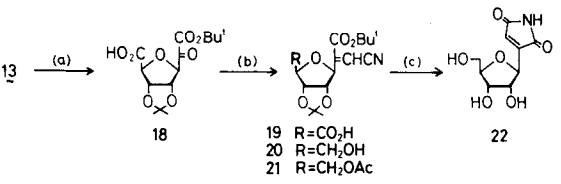


Scheme 2. Enantioselective synthesis of methyl L- and D-ribosides.

65–82° and the purified material recrystallized from $CHCl_3$–n-hexane (2:1) showed $[\alpha]_D^{22} + 73.8°$ (*c* 0.95, $CHCl_3$) and m.p. 92–93°. The ^1H NMR spectrum showed clearly retention of configuration[19] (Experimental), and the facile migration of tetrahydrofuran ring can be explained by participation of the O of the ring, contrary to the Baeyer–Villiger oxidation of ethyl pyruvate.[20] Treatment of **10**, $[\alpha]_D^{22} + 59.8°$, with dry HCl/MeOH at room temperature for 2 hr afforded **11** as colorless oil after usual workup and chromatography on silica gel. The methanolysis product **11** was reduced with $LiAlH_4$, and an oily material obtained upon workup was distilled under a reduced pressure to afford **12** in 67% yield from **9**, $[\alpha]_D^{20} + 63.2°$ (*c* 1.5, $CHCl_3$). The structure was proved to be chemically pure methyl 2,3-O-isopropylidene-β-ribofuranoside **12** by ^1H and ^{13}C NMR, and the L-configuration (with *ca* 77% ee) was established from the optical rotation by comparison with that of the corresponding derivative **17**, $[\alpha]_D^{20} - 82.2°$ (*c* 2.0, $CHCl_3$), obtained from natural D-ribose.[21] Therefore, the half-ester **4** enzymatically generated is also considered to be about 77% ee, since no resolution procedure was carried out during the chemical transformations. It was found best to use the recrystallized **10** ($[\alpha]_D^{22} + 73.8°$) for the synthesis of optically pure **12** (98% ee). The result mentioned above presents a good way to make L-ribose rarely found in nature, but it became necessary to convert the L-enantiomer to the D-enantiomer or **12** to **17** for the synthesis of sugar moieties of usual nucleosides. It should be mentioned here that another characteristic feature of the present methodology is able to carry out the enantiomer conversion easily from a common intermediate **4**. Thus, t-butyl half-ester **13** was prepared in 91% yield by treatment of **4** with isobutene in the presence of a catalytic amount of H_2SO_4 followed by alkaline hydrolysis (0.25 N NaOH, 25°, 10 min), showing $[\alpha]_D^{20} + 49.4°$ (*c* 1.16, $CHCl_3$) and m.p. 109–110.5° after recrystallization from ether–n-hexane (3:2, 77% recrystallization yield). Before the alkaline hydrolysis step, the optical purity of the t-butyl methyl ester was reconfirmed by ^1H NMR using a chiral shift reagent, tris-[3 - (heptafluoropropylhydroxymethylene) - *d* - camphorato], europium(III), and the ratio of the enantiomers was found to be about 9:1 (about 80% ee well consistent with that determined by the chemical conversion to **12** mentioned above). Successive treatment of the recrystallized **13** with O_3, MCPBA, HCl–MeOH and $LiAlH_4$ afforded **14**, **15**, **16** and **17**, respectively. The synthetic **17** ($[\alpha]_D^{20} - 77.7°$) was obtained in 32% overall yields from **13** and confirmed to be methyl 2,3 - O - isopropylidene - β - D - ribofuranoside with an optical purity of about 95% ee by comparison with the natural derivative[21a] mentioned above.

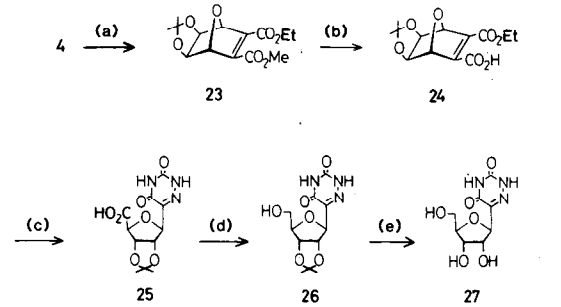
Enantioselective synthesis of (+)*-showdomycin and* (−)*-6-azapseudouridine* (*Scheme* 3 *and* 4)

The half-t-butyl ester **13** was considered to be a desired intermediate for the synthesis of showdomycin, since it can be easily converted to anomerically functionalized derivatives of tetrahydrofuran with the desired absolute configuration and the butyl ester is a preferred group to generate free acid under acidic conditions required at the final stage. (+)-Showdomycin (**22**) was synthesized in 9 steps



(a)O_3,AcOEt,−78°→refl. (b)1.$(EtO)_2P(O)CH_2CN$,NaH,cat.n-Bu_4NBr, DMSO 2.BH_3,THF 3.Ac_2O,Pyr. (c)1.CF_3CO_2H,$(CF_3CO)_2O$,50° 2.HCl, MeOH–H_2O(9:1)

Scheme 3. Enantioselective synthesis of (+)-showdomycin.



(a)$(EtO)_3CH$ (b)LiI,Pyr. (c)1.$O_3$2.$NH_2NHCONH_2$3.NaOMe (d)BH_3 (e)H^+

Scheme 4.
Enantioselective synthesis of (−) - 6 - azapseudouridine.

from **2** as shown in Scheme 3. The recrystallized t-butyl ester **13** was subjected to ozonolysis in ethyl acetate at −78° for 3 hr (1 g scale), and the resultant solution was warmed at reflux temperature for 1 hr, affording the decarboxylated cleavage product **18** in almost quantitative yield as an oily material. The most crucial step in this approach was the following Wittig reaction.

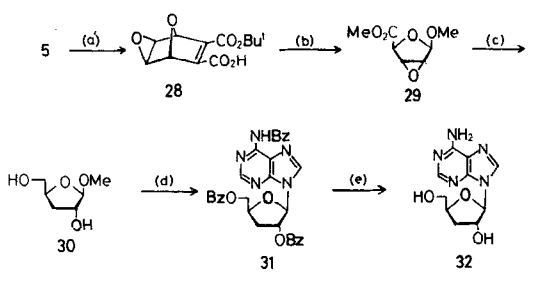
The reaction of **18** with diethyl cyanomethylphosphonate and NaH in DMSO proceeded smoothly only in the presence of n-Bu_4NBr under an atmosphere of argon (25°, 6 hr, 300 mg scale), affording the Wittig product **19** in 61% yield as a syrup after workup and chromatography on silica gel [$[\alpha]_D^{20} - 10.7°$ (*c* 1.0, $CHCl_3$); $R_f = 0.65$ (AcOEt–AcOH = 20:1)]. The role of the ammonium salt is considered to increase the nucleophilicity of the phosphonate anion after exchange of the counter ion.[22] Reduction of **19** with diborane afforded a primary alcohol **20** in 52% yield [$[\alpha]_D^{22} - 22.2°$ (*c* 0.57, $CHCl_3$); $R_f = 0.32$ (AcOEt–n-hexane = 1:1)]. After acetylation of **20** with Ac_2O (**21**, 96% yield), ring closure was effected with $(CF_3CO)_2O$ in CF_3COOH (50°, 8 hr, 200 mg scale), and removal of the protective groups with HCl in MeOH afforded **22** in 30% yield from **21**. The synthetic sample showed $[\alpha]_D^{23} + 49.1°$ (*c* 0.5, H_2O) well consistent with $[\alpha]_D^{22.5} + 49.9°$ (*c* 1, H_2O) of natural showdomycin,[23] and it was further confirmed to be identical with natural showdomycin spectroscopically (IR, ^1H NMR) and by the mixed m.p. method.

Next, 6-azapseudouridine was considered to be a good target to demonstrate the present chemicoenzymatic strategy, since the α-keto ester moiety derived from **2** in a most straightforward manner, is a versatile intermediate for the synthesis of other

C-nucleosides having different base residues.[24] For this synthetic purpose, the t-butyl ester **18** was considered unfavorable, because the final stage requires a basic condition[24c] for the intramolecular condensation between the ester group and the semicarbazino group. Therefore, another enantiomer conversion was investigated (Scheme 4). The half-ester **4** was treated with ethyl orthoformate (2 equiv, 130°, 2 hr) to afford ethyl methyl diester **23** $[\alpha]_D^{20} - 1.4°$ (*c* 5.5, $CHCl_3$). The selective cleavage of the methyl ester with LiI-pyridine[25] afforded the half ester **24** in 72% yield as colorless syrup, $[\alpha]_D^{20} + 39.9°$ (*c* 1.5, $CHCl_3$). Successive treatment of **24** with ozone and semicarbazide, and ring closure with sodium methoxide gave the compound **25** in 41% yield from **24**. Reduction of **25** with diborane yielded the isopropylidene derivative **26** in 61% yield as a colorless syrup, $[\alpha]_D^{20} - 41.2°$ (*c* 0.34, MeOH). The protective group of the vicinal glycol of **26** was removed with dil. HCl in methanol, affording (−)-6-azapseudouridine in 63% yield, $[\alpha]_D^{22} - 22°$ (*c* 0.16, H_2O). The synthetic sample (7 steps from **4**) was found to be about 88% ee on the basis of a reported value.[24a]

Enantioselective synthesis of cordycepin (3′-deoxyadenosine, Scheme 5)

The epoxy half-ester **5** was considered to be a good starting material for the synthesis of N-nucleosides having a different sugar moiety. Cordycepin, known as an inhibitor of RNA synthesis,[2a] was selected as a synthetic target of a N-nucleoside with a 3-deoxyribose moiety. The epoxy half-ester **5** was assumed to have the same absolute configuration as **4**, since the association and orientation of **2** and **3** at the active site of the enzyme may be similar to each other. The enantiomer conversion from **5** to **28** was effected by treatment with excess oxalyl chloride followed by esterification with t-BuOLi and alkaline hydrolysis (1 N NaOH, aqueous acetone, 5°, 20 min, 200 mg scale). It should be mentioned here that compounds of the epoxy series were found quite unstable to acidic conditions. For instance, the same treatment of **3** as of **2** with isobutene in the presence of p-toluenesulfonic acid resulted in easy cleavage t-Butyl half-ester **28** was obtained in 56% yield from **5**, showing m.p. 121–124° and $[\alpha]_D^{20} + 33°$ (*c* 0.5, $CHCl_3$). Successive treatment of **28** as described above (ozonolysis, Baeyer–Villiger reaction, and methanolysis) afforded **29** in 18% yield from **28**. Reduction of **29** with LAH gave exclusively methyl-3-deoxy-β-D-ribofuranoside in 79% yield, a known precursor of cordycepin,[26] $[\alpha]_D^{20} - 63°$ (*c* 0.4, $CHCl_3$). In order to determine the optical purity of **28**, the furanoside **30** was converted to the 3′-deoxynucleoside **32** via **31**, according to the procedures by Walton *et al.* Cordycepin, synthesized in 12 steps from **3**, showed m.p. 222–224°, $[\alpha]_D^{20} - 34°$ (*c* 0.25, H_2O), and was found to be about 77% ee on the basis of a reported value.[26] The key features of the present methodology include the following: (1) pig liver esterase efficiently hydrolyzed unsaturated meso and rather rigid compounds **2** and **3** with high optical purity of synthetic value; (2) it was found that half-esters **4** and **5** formed enzymatically correspond to the L-series sugar moiety of nucleosides and the half-esters were successfully converted to the D-series sugar moiety (enantiomer conversion; **4–13** and **5–28**); (3) a combination of asymmetric hydrolysis (enzyme process) and decarboxylative ozonolysis directly provided a versatile intermediate **18** applicable to the synthesis of various C-nucleosides; (4) highly selective Baeyer–Villiger oxidation made it possible to elaborate various types of sugar moiety including L- and D-riboses and 3-deoxyribofuranoside. Further investigation of the present chemicoenzymatic approach to carbocyclic nucleosides are in progress in our laboratory, and the results will be reported soon.[27]



(a) 1.$(COCl)_2$,CH_2Cl_2,refl.2.1-BuOH,n-BuLi,THF,0° 3.NaOH,aq.Acetone (b) 1.O_3,MeOH,−78° 2.MCPBA,$CH_2Cl_2$3.MeOH,p-TsOH (c)$LiAlH_4$ (d)1.BzCl,Pyr. 2.AcBr,30%HBr–AcOH 3.Chloromercuri-N^6-bezoyladenine (e)NaOMe,MeOH,refl.

Scheme 5. Enantioselective synthesis of (−)-cordycepin.

EXPERIMENTAL

M.ps were measured on a Yamato MP-21 apparatus and were uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on a JEOL FX-100 spectrometer and chemical shifts are expressed in ppm downfield from TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a JASCO A-102 spectrometer. MS were measured with a JEOL JMS-01 SG-2 mass spectrometer. Optical rotations were measured with a JASCO DIP-104 digital polarimeter. Silica gel (Wacogel C-200) was used for column chromatography and silica gel (Kiesel gel 60 F254, Merck) for TLC.

Dimethyl exo - 5,6 - dimethylmethylenedioxy - 7 - oxabicycle[2.2.1]*hept - 2 - ene - 2,3 - dicarboxylate* (**2**)

To a soln of 22.3 g (165 mmol) of N-methylmorpholine-N-oxide in 300 mL of t-BuOH and 30 mL of water was added dropwise 20 mL (0.8 mmol) of osmium tetroxide-t-BuOH soln (4×10^{-2} mmol/mL) at room temp under argon. To the soln was added dropwise 33 g (157 mmol) of **1** in 100 mL of THF over 1.5 hr. After being stirred for 3.5 hr at room temp, the mixture was filtered and the solvent was evaporated to dryness. The residue was extracted with Et-OAc and the organic layer was washed with 2M HCl. Workup as usual afforded the crude diol which was purified by a silica gel column chromatography using n-hexane–AcOEt (3:1) as eluant to give 21.3 g of the pure diol in 55.4% yield as colorless syrup. To a soln of 21.3 g (86.9 mmol) of diol in 192 mL acetone and 64 mL 2,2-dimethoxypropane was added 50 mg of *p*-toluenesulfonic acid. The mixture was stirred for 3 hr at room temperature and passed through a short silica gel column chromatography. The solvent was evaporated to dryness. Purification on a silica gel column chromatography gave 21.1 g (85%) of the acetonide **2** as white crystals: m.p. 74–75°; (Found: C, 55.05; H, 5.73. Calc. for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67%).

Dimethyl 5,6 - exo - *epoxy* - 7 - *oxabicyclo*[2.2.1]*hept* - 2 - *ene* - 2,3 - *dicarboxylate* (**3**)

To a soln of 222 mg (1.06 mmol) of **1** in 2.5 mL $CHCl_3$ was added portionwise 250 mg (1.2 mmol) of MCPBA (85%). The mixture was stirred at room temp for 3 hr and the ppt

formed was removed by filtration. The filtrate was concentrated to dryness and the residue was recrystallized from ether. The epoxide **3** (184 mg) was obtained as white crystals in 77% yield: m.p. 93–94°; IR (KBr) 1730, 1630 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 3.78 (s, 2H), 3.85 (s, 2H), 5.14 (s, 2H); (Found: C, 53.16; H, 4.50. Calc. for $C_{10}H_{10}O_6$: C, 53.14; H, 4.46%).

(1S,4R,5R,6S) - 5,6 - *Dimethylmethylenedioxy* - 3 - *methoxycarbonyl* - 7 - *oxabicyclo*[2.2.1]*hept* - 2 - *ene* - 2 - *carboxylic acid* (**4**)

To a soln of 3 g (10.6 mmol) of **2** in 30 mL acetone and 300 mL 0.1 M phosphate buffer (pH 8) was added 3 mL (4140 units) pig liver esterase. The mixture was incubated for 4 hr at 32°, and then acidified to pH 4 with 2 M HCl and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to afford 2.73 g (96%) of **4** as white solid [$[\alpha]_D^{20} - 37.1°$ (*c* 1.0, $CHCl_3$)]. It was dissolved in hot CCl_4 and standing the soln at room temp deposited a small amount of a solid material of very low optical purity [$[\alpha]_D^{20} - 10.6$ (*c* 1.0, $CHCl_3$)] and then the solid was removed by filtration. The filtrate was concentrated and recrystallized two times from CCl_4–n-hexane (2:1): $[\alpha]_D^{20} - 49°$ (*c* 1.0, $CHCl_3$); m.p. 115.5–117.5°; IR (KBr) 1725, 1650, 1622 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.37 (s, 3H), 1.52 (s, 3H), 4.00 (s, 3H), 4.54 (s, 2H), 5.20 (s, 1H), 5.24 (s, 1H); (Found: C, 53.39; H, 5.25. Calc for $C_{12}H_{14}O_7$: C, 53.33; H, 5.22%).

(1S,4R,5R,6S) - 5,6 - *Epoxy* - 3 - *methoxycarbonyl* - 7 - *oxabicyclo*[2.2.1]*hept* - 2 - *ene* - 2 - *carboxylic acid* (**5**)

To an emulsion of 51.1 mg (0.226 mmol) of **3** in 10 mL 0.1 M phosphate buffer (pH 8) was added 50 μL (65 units) pig liver esterase. The mixture was incubated for 7 hr at 20°, and then acidified with 2 M HCl and extracted with EtOAc several times. Workup as usual afforded 48.1 mg of **5** as white solid in quantitative yield: $[\alpha]_D^{20} - 23°$ (*c* 0.52, $CHCl_3$); m.p. 120–122°; IR (KBr) 3350, 1725, 1670, 1615 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 3.80 (s, 2H), 4.03 (s, 3H), 5.23 (s, 1H), 5.42 (s, 1H); (Found: C, 50.69; H, 3.79. Calc for $C_9H_8O_6$: C, 50.95; H, 3.80%).

Methyl (2R,3R,4S,5S) - 3,4 - *dimethylmethylenedioxy* - 5 - *methoxalyl* - 2,3,4,5 - *tetrahydrofuran* - 2 - *carboxylate* (**9**)

To a soln of 131 mg (0.485 mmol) of **4** [$[\alpha]_D^{20} - 37.1°$] in 3 mL MeOH was bubbled through O_3 for 15 min at −78°, and then N_2 for 15 min. The soln was allowed to stand at room temp and the solvent was concentrated *in vacuo* to afford 140 mg of **9** as colorless syrup in quantitative yield. The ketoester **9** was directly used without further purification for the next step: $R_f = 0.66$ (AcOEt/n-hexane = 1/1); IR ($CHCl_3$) 1742, 1382, 1371 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.36 (s, 3H), 1.52 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 4.4–5.3 (m, 4H).

Methyl (2R,3R,4S,5R) - 3,4 - *dimethylmethylenedioxy* - 5 - *methoxalyloxy* - 2,3,4,5 - *tetrahydrofuran* - 2 - *carboxylate* (**10**)

To a soln of 715 mg (2.48 mmol) of **9** in 5 mL dry CH_2Cl_2 was added dropwise 640 mg (3.2 mmol) MCPBA (85%) in 5 mL dry CH_2Cl_2 at room temp. After being stirred for 1.5 hr at room temp, the mixture was washed with a cold satd $NaHSO_3$ aq, a satd $NaHCO_3$ aq and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford 578 mg (77%) of **10** as white solid; $[\alpha]_D^{22} + 59.8°$ (*c* 1.04, $CHCl_3$); m.p. 65–82°; It was recrystallized from $CHCl_3$–n-hexane (2:1): m.p. 92–93°; $[\alpha]_D^{22} + 73.8°$ (*c* 0.95, $CHCl_3$); IR (KBr) 1740, 1760 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.32 (s, 3H), 1.51 (s, 3H), 3.75 (s, 3H), 3.90 (s, 3H), 4.79 (s, 1H), 4.82 (d, J = 5.5 Hz, 1H), 5.26 (d, J = 5.5 Hz, 1H), 6.32 (s, 1H); (Found: C, 47.12; H, 5.14. Calc for $C_{12}H_{16}O_9$: C, 47.37; H, 5.30%).

Methyl (2R,3R,4S,5S) - 3,4 - *dimethylmethylenedioxy* - 5 - *methoxy* - 2,3,4 - 5 - *tetrahydrofuran* - 2 - *carboxylate* (**11**)

To a soln of 502 mg (1.66 mmol) of **10** ($[\alpha]_D^{22} + 59.8°$) in 10 mL dry MeOH was added dropwise 2 mL of a MeOH soln saturated with HCl. After allowing to stand at room temp for 2 hr, the solvent was evaporated *in vacuo* to dryness. The residue was dissolved in 5 mL dry acetone and 1 mL 2,2-dimethoxypropane. To the soln was added 50 mg *p*-toluenesulfonic acid. After being stirred at room temp for 1 hr, the mixture was poured into a satd $NaHCO_3$ aq and extracted with $CHCl_3$ several times. Workup as usual afforded **11** which was purified by a silica gel column chromatography using ether–n-hexane (1:1) as eluant to give 291 mg (72%) pure **11** as colorless syrup: $R_f = 0.52$ (ether/n-hexane = 1/1); IR (neat) 1730, 1385, 1378 cm^{-1}

Methyl 2,3 - O - *isopropylidene* - β - L - *ribofuranoside* (**12**)

To an emulsion of 69 mg (1.7 mmol) LAH in 1 mL dry ether was added dropwise 284 mg (1.16 mmol) **11** in 3 mL dry ether under argon. The mixture was heated under reflux for 25 min and then cooled at room temp. To the soln was added dropwise carefully 0.1 mL water and 0.2 mL of 2.5 M NaOH and the white ppt formed was removed by filtration. The filtrate was dried over Na_2SO_4 and the solvent was evaporated to dryness. The residue after distillation under a reduced pressure gave 219 mg of **12** in 93% yield as colorless oil. The synthetic sample **12** was confirmed to be identical in all respects except the optical rotation with the sample derived from natural D-ribose.b.p. 110°/0.3 mmHg; $[\alpha]_D^{20} + 63.2°$ (*c* 1.5, $CHCl_3$); $R_f = 0.66$ ($CHCl_3$/MeOH = 19/1) IR (neat) 3420, 1380, 1368 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.32 (s, 3H), 1.48 (s, 3H), 3.36 (br, 1H), 3.68 (m, 2H), 4.40 (t of dd, J = 3 Hz, 1H), 4.58 (d, J = 6 Hz, 1H), 4.82 (d, J = 6 Hz, 1H), 4.97 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS) δ 25.0, 26.5, 55.8, 64.2, 82.2, 86.4, 88.8 110.6, 112.7.

(1R,4S,5S,6R) - 3 - *t* - *Butoxycarbonyl* - 5,6 - *dimethylmethylenedioxy* - 7 - *oxabicyclo*[2.2.1]*hept* - 2 - *ene* - 2 - *carboxylic acid* (**13**)

To a soln of 1.77 g (6.55 mmol) of **4** in 20 mL dry CH_2Cl_2 was added 2 mL (21 mmol) isobutene and 40 mg (0.4 mmol) conc H_2SO_4 at −78°. The mixture was stirred at room temp for 16 hr in a sealed tube, poured into a cold satd $NaHCO_3$ aq and extracted with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to dryness to afford 1.6 g (75%) of **4** as colorless syrup. The aqueous layer was acidified to pH 3 with 2M HCl and extracted with CH_2Cl_2. Workup as usual afforded 310 mg (18%) of starting **4** (91% yield based on the recovered **4**). The butylester of **4** (1.6 g, 4.9 mmol) was dissolved in 29 mL acetone and to the soln was added dropwise 29 mL (7.45 mmol) 0.25 M NaOH at 0–5°. After being stirred for 1 hr at room temp, the mixture was acidified to pH 5 with 2M HCl and extracted with CH_2Cl_2. Workup as usual afforded 1.47 g (96%) of **13** as white solid [$[\alpha]_D^{20} + 39.6°$ (*c* 0.85, $CHCl_3$)]. It was recrystallized from ether–n-hexane (3:2): m.p. 109–110.5°; $[\alpha]_D^{20} + 49.4°$ (*c* 1.16, $CHCl_3$); IR (KBr) 1740, 1720, 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.38 (s, 3H), 1.52 (s, 3H), 1.58 (s, 9H), 4.53 (s, 2H), 5.10 (s, 1H) 5.20 (s, 1H); Ms (*m/e*) 313 ($M^+ + 1$); (Found: C, 57.52; H, 6.46. Calc for $C_{15}H_{20}O_7$: C, 57.58; H, 6.46%).

Methyl 2,3 - O - *isopropylidene* - β - D - *ribofuranoside* (**17**)

The ribofuranoside **17** (150 mg) was obtained as colorless oil in 32% yield from the recrystallized **13** ($[\alpha]_D^{20} + 49.4°$ 725 mg, 2.32 mmol) by the same procedures described in the case of **12**. The synthetic **17** was found to be 95% ee [$[\alpha]_D^{20} - 77.7°$ (*c* 1.5, $CHCl_3$)] and confirmed to be identical in all spectrum data with the natural derivative [$[\alpha]_D^{25} - 82.2°$ (*c* 2.0, $CHCl_3$)] from D-ribose.[21a]

(2S,3S,4R,5R) - 5 - *t* - *Butoxalyl* - 3,4 - *dimethylmethylenedioxy* - 2,3,4,5 - *tetrahydrofuran* - 2 - *carboxylic acid* (**18**)

To a soln of 1.05 g (3.36 mmol) of **13** in 30 mL EtOAc was bubbled through O_3 for 30 min at −78° and then N_2 for 15 min. The soln was refluxed for 1 hr, evaporated to dryness to give 1.06 g of **18** in quantitative yield. The ketoester **18** was used without further purification for the next step; IR ($CHCl_3$) 1740, 1723, 1706, 1380 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.39 (s, 3H), 1.53 (s, 3H), 1.58 (s, 9H), 4.4–5.4 (m, 4H).

t - Butyl (Z) - 2 - [(2S,3S,4S,5S) - 5 - *carboxy* - 3,4 - *dimethylmethylenedioxy* - 2,3,4,5 - *tetrahydrofuran* - 2 - *yl*]- 3 - *cyanoacrylate* (**19**)

To an emulsion of 269 mg (6.72 mmol) of NaH (60%) in 18 mL dry DMSO was added dropwise 1.43 (8.06 mmol) of $(EtO)_2P(O)CH_2CN$ at room temp under argon. After being stirred at room temp for 1 hr, it was added dropwise to a soln of 1.06 g (3.36 mmol) of **18** and 148 mg (0.46 mmol) n-Bu_4NBr in 15 mL dry DMSO under argon. After being stirred at room temp for 5 hr, the mixture was poured into 70 mL 1M KH_2PO_4 soln and extracted with EtOAc. Workup as usual afforded the crude **19** which was purified by a silica gel column chromatography using benzene–EtOAc–AcOH (100:50:1) as eluant to give 665 mg (61%) of **19** as colorless syrup: $R_f = 0.65$ (AcOEt/AcOH = 50/1); $[\alpha]_D^{20} - 10.7°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2240, 1710, 1380 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.40 (s, 3H), 1.60 (s, 12H), 4.70 (m, 2H), 4.99 (m, 2H), 6.46 (d, J = 1.3 Hz, 1H), 8.70 (br, 1H).

t - Butyl (Z) - 2 - (2,3 - O - *isopropylidene* - β - D - *ribofuranosyl*) - 3 - *cyanoacrylate* (**20**)

To a soln of 540 mg (1.59 mmol) of **19** in 10 mL dry THF was added 1 mL (2.1 mmol) BH_3-THF soln (2.06 mmol/mL) at 0° under argon. The mixture was stirred for 2 hr at room temp and cooled with ice water. To the soln was added dropwise 0.5 mL water and the solvents were evaporated as well as possible. The residue was further dissolved in MeOH and a trace amount of water of the product was removed by coevaporation with MeOH. The residue was purified by a silica gel column chromatography using n-hexane–EtOAc (2:1) as eluant to give 268 mg (52%) of **20** as colorless syrup: $R_f = 0.32$ (AcOEt/n-hexane = 1/1); $[\alpha]_D^{22} - 22.2°$ (*c* 0.57, $CHCl_3$), IR (neat) 3460, 2205, 1709, 1624 cm^{-1}, ^1H NMR ($CDCl_3$/TMS) δ 1.35 (s, 3H), 1.59 (s, 12H), 3.68 (dd, J = 3 Hz, 1H), 3.86 (dd, J = 3, 12 Hz, 1H), 4.14 (m, 1H), 4.48–4.9 (m, 3H), 6.11 (d, J = 1.3 Hz, 1H).

t-Butyl (Z) - 2 - (5 - O - *acetyl* - 2,3 - O - *isopropylidene* - β - D - *ribofuranosyl*) - 3 - *cyanoacrylate* (**21**)

To a soln of 210 mg (0.645 mmol) of **20** in 2 mL dry pyridine was added 2 mL Ac_2O. The mixture was stirred at room temp for 2 hr, poured into a satd $NaHCO_3$ aq and extracted with benzene. The organic layer was washed with 2 M HCl and water. Workup as usual afforded 228 mg (96%) of **21** as colorless syrup; $R_f = 0.58$ (AcOEt/n-hexane = 1/1); IR (neat) 2225, 1740, 1720, 1630 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.35 (s, 3H), 1.58 (s, 12H), 2.09 (s, 3H), 4.05–4.41 (m, 3H), 4.44–4.68 (m, 2H), 4.81 (dd, J = 2, 3 Hz, 1H), 6.04 (d, J = 2 Hz, 1H).

Showdomycin (**22**)

The acetate **21** (210 mg, 0.57 mmol) was dissolved 1 mL trifluoroacetic acid and 2 mL trifluoroacetic anhydride. The mixture was heated at 40–50° for 8 hr under argon in a sealed tube. After being cooled, the mixture was poured into a satd $NaHCO_3$ aq, extracted with EtOAc. Workup as usual afforded 140 mg crude acetate of showdomycin which was purified by silica gel preparative TLC using ether–n-hexane (4:1) as eluant to give 64 mg (36%) of the pure acetate as colorless syrup. The acetate (64 mg) was dissolved in 1 mL MeOH and added 0.1 mL of conc HCl. The mixture was allowed to stand at room temp for 16 hr, and the solvent was evaporated to dryness. The residue was recrystallized from i-PrOH to give 37.1 mg pure showdomycin as white crystals (28% yield from **21**): The synthetic sample **22** was confirmed to be identical in all respects with the natural showdomycin.[23] $[\alpha]_D^{23} + 49.1°$ (*c* 0.5, H_2O); m.p. 149–153° (Found: C, 46.87; H, 4.79; N, 5.91. Calc for $C_9H_{11}O_6N$: C, 47.16; H, 4.84; N, 6.11%).

Methyl (1R,4S,5S,6R) - 3,4 - *dimethylmethylenedioxy* - 3 - *ethoxycarbonyl* - 7 - *oxabicyclo*[2.2.1]*hept* - 2 - *ene* - 2 - *carboxylate*

The half ester **4** (280 mg, 1.04 mmol) was dissolved in 0.35 mL (2.1 mmol) ethyl orthoformate and the mixture was heated at 130° for 2 hr. The solvent was evaporated to dryness. Purification on a silica gel column chromatography using ether–n-hexane (1:2) as eluant gave 292 mg of **23** in 94% yield as colorless oil: $[\alpha]_D^{20} - 1.4°$ (*c* 5.5, $CHCl_3$); ^1H NMR ($CDCl_3$/TMS) δ 1.29 (s, 3H), 1.34 (t, 3H), 1.44 (s, 3H), 3.79 (s, 3H), 4.25 (q, 2H), 4.47 (s, 2H), 4.90 (s, 2H).

(1R,4S,5S,6R) - 5,6 - *Dimethylmethylenedioxy* - 3 - *ethoxycarbonyl* - 7 - *oxabicyclo*[2.2.1]*hept* - 2 - *ene* - 2 - *carboxylic acid* (**24**)

To a soln of 1.08 g (8.1 mmol) anhyd LiI in 10 mL dry pyridine was added 803 mg (2.69 mmol) of **23** in 5 mL pyridine. The mixture was heated under reflux for 55 min. After being cooled, the mixture was poured into ice water, and extracted with EtOAc. The organic layer was washed with 2 M HCl. Workup as usual afforded 724 mg crude **24** which was purified by a silica gel column chromatography using AcOEt–AcOH (49:1) as eluant to give 484 mg pure **24** in 72% yield based on the recovered **23** (96 mg, 12%) as colorless syrup: $[\alpha]_D^{20} + 39.9°$ (*c* 1.5, $CHCl_3$); IR (neat) 3330, 1730, 1675 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.36 (s, 3H), 1.40 (t, 3H), 1.52 (s, 3H), 4.42 (q, J = 7 Hz), 4.53 (s, 2H), 5.14 (d, J = 1.5 Hz, 1H), 5.20 (d, J = 1.5 Hz, 1H).

6 - [(2S,3S,4S,5S) - 5 - *Carboxy* - 3,4 - *dimethylmethylenedioxy* - 2,3,4,5 - *tetrahydrofuran* - 2 - *yl*] - 2,3,4,5- *tetrahydro* - 1,2,4 - *triazin* - 3,5 - *dione* (**25**)

To a soln of 403 mg (0.35 mmol) of **24** in 10 mL EtOAc was bubbled through O_3 for 30 min at −78° and then N_2 for 30 min. The solvent was evaporated to dryness and the residue was dissolved in 10 mL MeOH. To the soln was added dropwise 234 mg (2.1 mmol) semicarbazide hydrochloride and 172 mg (2.1 mmol) NaOAc in 2 mL water. The mixture was heated under reflux for 3.5 hr and the solvent was evaporated to dryness. Purification on a short silica gel column chromatography using EtOAc–EtOH–water (3:1:1) as eluant gave 530 mg crude semicarbazone. It was dissolved in 6 mL MeOH and 3 mL MeOH soln of 1 M NaOMe was added to the soln. The mixture was heated under reflux for 2 hr, cooled with ice water, and then acidified with 2 M HCl. After extraction with EtOAc, the solvent was dried over Na_2SO_4 and evaporated to dryness. Workup as usual gave 330 mg crude **25** which was purified by a silica gel column chromatography using EtOAc–AcOH (49:1) as eluant to give 174 mg pure **25** as white crystals in 41% yield, m.p. > 218° (dec); $[\alpha]_D^{20} - 114.8°$ (*c* 0.6, MeOH); IR (KBr) 3400, 1720, 1685, 1380 cm^{-1}; ^1H NMR (CD_3OD/TMS) δ 1.36 (s, 3H), 1.51 (s, 3H), 4.52 (d, J = 1.3 Hz, 1H), 5.18 (m, 3H); Ms (*m/e*) 299 (M^+), 283, 196, 139.

6 - (2,3 - O - *isopropylidene* - β - D - *ribofuranosyl*) - 2,3,4,5 - *tetrahydro* - 1,2,4 - *triazin* - 3,5 - *dione* (**26**)

To a soln of 98 mg (0.35 mmol) of **25** in 1 mL dry THF was added dropwise 1.5 mL (1.65 mmol) BH_3-THF soln (1.1 mmol/mL) at 0–5° under argon. After being stirred for 2 hr at 0–5°, 0.1 mL water was added to the soln. The solvent was evaporated to dryness. The residue was purified by a silica gel column chromatography using EtOAc as eluant to give 57 mg of **26** in 61% yield as colorless syrup: $[\alpha]_D^{20} - 41.2°$ (*c* 0.34, MeOH); IR (KBr) 3230, 1685, 1382, 1372 cm^{-1}; ^1H NMR (CD_3OD/TMS) δ 3.64 (dd, J = 4.2 Hz,

1H), 3.80 (dd, J = 3.6, 12 Hz, 1H), 4.1–4.4 (m, 1H), 4.7–5.1 (m, 3H).

6-Azapseudouridine (**27**)

To a soln of 57 mg (0.21 mmol) of **26** in 1 mL MeOH was added 0.3 mL of 2 M HCl. The mixture was stirred for 16 hr at room temp, and the solvent was evaporated to dryness. The residue was crystallized from EtOH–CH_2Cl_2. The pure **26** (39.8 mg) was obtained as white crystals in 63% yield: $[\alpha]_D^{22} - 22°$ (*c* 0.16, H_2O); m.p. 136°C (dec) (lit. m.p. 139–140°, $[\alpha]_D^{25} - 24.9°$).[24a]

(1R,4S,5S,6R) - 3 - *t* - *Butoxycarbonyl* - 5,6 - *epoxy* - 7 - *oxabicyclo*[2.2.1]*hept* - 2 - *ene* - 2 - *carboxylic acid* (**28**)

To an emulsion of 212 mg (1.0 mmol) of **5** in 3 mL dry CH_2Cl_2 was added dropwise 0.5 mL (5.9 mmol) oxalyl chloride under argon. The mixture was heated under reflux for 4 hr and the solvent was evaporated to dryness. The residue was dissolved in 3 mL dry THF and to the soln was added dropwise 111 mg (1.5 mmol) t-BuOH in 1 mL dry THF and 1 mL (1.48 mmol) n-BuLi in hexane at 0–5°. After being stirred for 20 min at room temp, the mixture was poured into ice water and extracted with CH_2Cl_2. Workup as usual afforded the crude butylester which was purified by a silica gel column chromatography using ether–n-hexane (1:1) as eluant to give 143 mg (53%) of **28** as colorless syrup. To a soln of 143 mg (0.53 mmol) of **28** in 3 mL acetone was added dropwise 0.58 mL (0.58 mmol) 1 M NaOH at 0–5°. After being stirred for 20 min at 0–5°, the mixture was acidified to pH 2 with 2 M HCl and then extracted with CH_2Cl_2. Workup as usual afforded 120 mg (90%) of **28** as white crystals: m.p. 121–124°; $[\alpha]_D^{20} + 33°$ (*c* 0.5, $CHCl_3$); IR (KBr) 3350, 1735, 1630, 1610 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.61 (s, 9H), 3.77 (s, 1H), 3.80 (s, 1H), 5.15 (s, 1H), 5.30 (s, 1H); (Found: C, 56.60; H, 5.56. Calc for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55%).

Methyl (2S,3S,4R,5R) - 3,4 - *epoxy* - 5 - *methoxy* - 2,3,4,5 - *tetrahydrofuran* - 2 - *carboxylate* (**29**)

To a soln of 100 mg (0.393 mmol) of **28** in 2.5 mL MeOH was bubbled through O_3 for 15 min at −78°, and then N_2 for 15 min. After complete removal of the solvent, the residue was dissolved in 2 mL dry CH_2Cl_2. To the soln was added portionwise 95 mg (0.47 mmol) MCPBA and the mixture was stirred for 16 hr at room temp, washed with a sat $NaHSO_3$ aq and a sat $NaHCO_3$ aq. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in 1.5 mL MeOH and to the soln was added 6 mg (0.03 mmol) *p*-toluenesulfonic acid hydrate. After being stirred for 16 hr at room temp, the mixture was extracted with CH_2Cl_2 several times. Workup as usual afforded crude **29** which was purified by a silica gel column chromatography using n-hexane–ether (2:1) as eluant to give 12 mg (18%) of **29** as colorless syrup: $[\alpha]_D^{20} - 63°$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$/TMS) δ 3.44 (s, 3H), 3.64 (d, J = 3 Hz, 1H), 3.75 (s, 3H), 4.01 (d, J = 3 Hz, 1H), 4.56 (s, 1H), 4.98 (s, 1H).

Methyl 3-deoxy-β-D-ribofuranoside (**30**)

To a soln of 212.4 mg (1.22 mmol) of **29** in 5 mL dry THF was added portionwise 97.2 mg (2.56 mmol) LAH under argon. The mixture was stirred for 16 hr at room temp. To the soln was added dropwise carefully 1.5 mL i-PrOH and 4 mL water. The ppt was removed by filtration and the filtrate was neutralized with IRC-50(H^+) resin. Purification on a silica gel column chromatography using CH_2Cl_2–MeOH (49:1) as eluant gave **30** (143.4 mg) in 79% yield as colorless oil: The optical rotation of the crude material was found levo rotary, but it was used for the next step without further purification. IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.85 (ddd, J = 1.5, 7, 13.5 Hz, 1H), 2.10 (dd, J = 4.5, 13.5 Hz, 1H), 3.36 (s, 3H), 3.43 (dd, J = 5, 11.5 Hz, 1H), 3.69 (dd, J = 3, 11.5 Hz, 1H), 4.20 (dd, J = 1.5, 4.5 Hz, 1H), 4.48 (ddd, J = 3, 5, 7 Hz, 1H), 4.76 (s, 1H); Ms (*m/e*) 148 (M^+), 130 (M^+-H_2O), 117 (M^+-OMe), 98 (M^+-MeOH-H_2O).

N^6,2',5' - *Tribenzoyl* - 3' - *deoxyadenosine* (**31**)

To a soln of 94.1 mg (0.635 mmol) of **30** in 1 mL dry pyridine was added dropwise 0.2 mL (1.3 mmol) benzoyl chloride. After being stirred for 16 hr at room temp, the solvent was evaporated to dryness. Purification on a silica gel preparative TLC using n-hexane–ether (4:1) as eluant gave 187 mg of dibenzoate in 83% yield as white solid. To a soln of 108.6 mg (0.305 mmol) dibenzoate in 0.5 mL AcOH was added dropwise 35 μL (0.187 mmol) acetyl bromide and 0.5 mL 30% hydrobromide-AcOH. After being stirred for 20 min at room temp, the solvents were evaporated as well as possible. The residue was several times coevaporated with toluene to dryness. The residue dissolved in 3 mL toluene was added dropwise to a soln of 150 mg (0.316 mmol) chloromercuri - N^6 - benzoyladenine in 6 mL xylene. After the mixture was heated under reflux for 30 min, the insoluble material was removed by filtration. To the filtrate was added 20 mL petroleum ether, and the deposited ppt was filtered off and washed with petroleum ether. The ppt was dissolved in $CHCl_3$ and washed with 30% KI aq. Purification on silica gel preparative TLC using CH_2Cl_2–MeOH (100:1) as eluant gave 35.7 mg of **31** in 21% yield: IR (KBr) 1720, 1610, 1585, 1455 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 2.50 (ddd, J = 1, 5.5, 13.5 Hz, 1H), 3.01 (ddd, J = 5.5, 10, 13.5 Hz, 1H), 4.54 (m, 2H), 4.87 (m, 1H), 6.09 (dd, J = 1, 5.5 Hz, 1H), 6.44 (d, J = 1 Hz, 1H), 7.2–8.1 (m, 16H), 8.17 (s, 1H), 8.70 (s, 1H); Ms (*m/e*) 563 (M^+), 458 (M^+-Bz), 325 (M^+-Ad^{Bz}).

Cordycepin (**32**)

To a soln of 23.3 mg (0.041 mmol) of **31** in 1.5 mL MeOH was added 23 mg (0.426 mmol) NaOMe. After being refluxed for 1 hr, the solvent was evaporated to dryness. The residue was dissolved in water and neutralized with AcOH. Purification on silica gel preparative TLC using $CHCl_3$–MeOH (10:1) as eluant gave 9.8 mg of **32** in 94% yield: The synthetic **32** was confirmed to be identical in all respects with the natural codycepin.[26] M.p. 222–224°; $[\alpha]_D^{20} - 34°$ (*c* 0.25, H_2O); IR (KBr) 3350, 3100, 1610, 1570 cm^{-1}; ^1H NMR (DMSOd^6/TMS) δ 1.91 (ddd, J = 3, 6, 13 Hz, 1H), 2.26 (ddd, J = 5.5, 8, 13 Hz, 1H), 4.36 (m, 1H), 4.58 (m, 1H), 5.86 (d, J = 3 Hz, 1H), 7.28 (s, 2H, NH_2), 8.12 (s, 1H), 8.34 (s, 1H); (Found: C, 47.63; H, 5.19; N, 27.60. Calc for $C_{10}H_{13}N_5O_3$; C, 47.80; H, 5.22; N, 27.88%)

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