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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 68

Acyclonucleosides: Part 2. *diseco*-Nucleosides*

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This chapter is the second of a sequence of three chapters that appears in successive volumes of this series dealing with the chemistry of acyclonucleosides. The first chapter appeared in the previous volume [97AHC391] and dealt with *seco*-nucleosides (one bond disconnection). This chapter deals with *diseco*-nucleosides (two bond disconnections). The final chapter of this series will deal with *tri*-, *tetra*-, and *pentaseco*-nucleosides, as well as contain an appendix of the literature that appeared after the three chapters were prepared.

III. *diseco*-Nucleosides from Two Bond Disconnections

Acyclonucleosides that are considered under this type of disconnection are those resulting from omitting any two bonds from the pentose. There are seven such types.

A. 1′,2′- AND 2′,3′-*diseco*-NUCLEOSIDES (TYPE 2.1)

The most important member is the guanine analog. There are various modifications under this type of acyclic nucleoside.

* Part 1 is in Volume 67 and Part 3 is in Volume 69.

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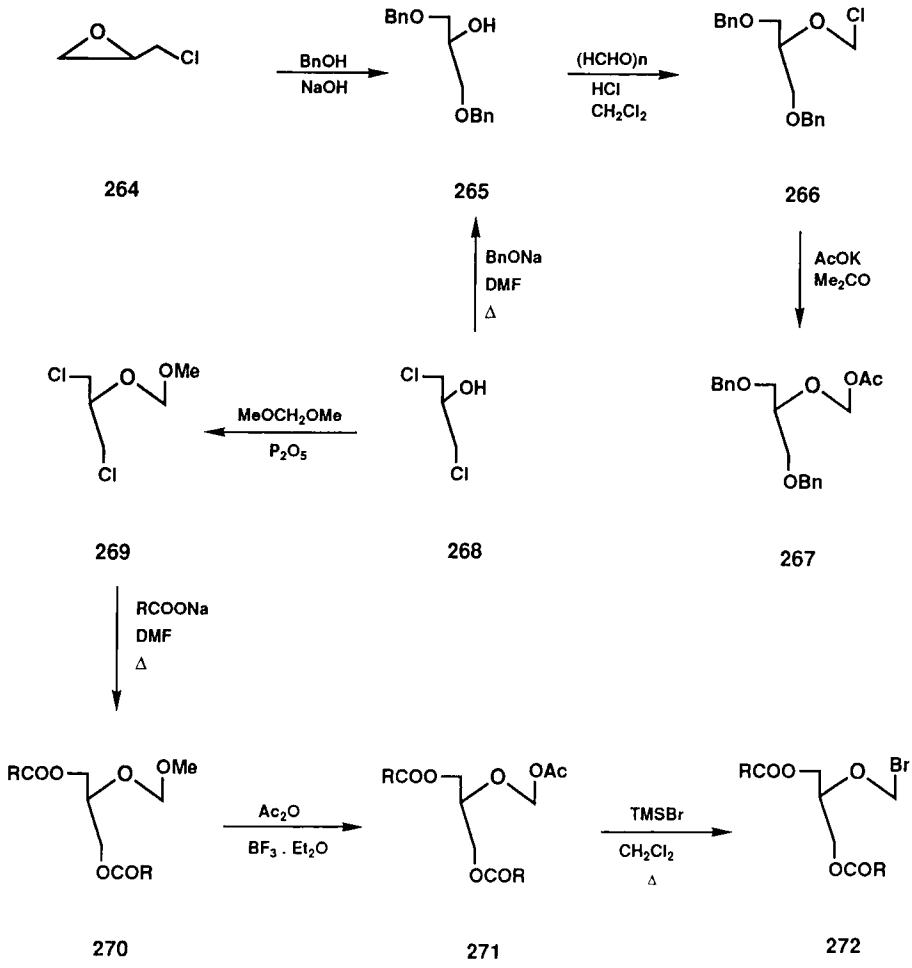
1. *General Methods for Construction*

Most of these methods involve the alkylation of the heterocyclic ring by a suitable alkoxy alkyl halide. Further modification on the heterocyclic rings may sometimes be used on a preformed acyclonucleoside. Thus, the chloromethyl ether **266** was prepared from epichlorohydrin (**264**) by treatment with benzyl alcohol and aqueous NaOH to give 1,3-di-*O*-benzylglycerol **265** (83JMC759). Alternatively, **265** was prepared from 1,3-dichloro-2-hydroxypropane **268** (84CJC241). Chloromethylation of **265** gave **266,** whose treatment with potassium acetate gave 2-*O*-(acetoxymethyl)-1, 3-di-*O*-benzylglycerol (**267**) (83JMC759). The choice of the hydroxy protecting groups must be made to avoid difficulties encountered with the removal of the benzyl groups during the subsequent steps, particularly in the cytosine series. Thus, the requisite acyclic chain **272** was prepared by commencing with 1,3-dichloro-2-propanol **268.** Methoxymethylation of **268** gave **269,** where this group served a dual purpose. It protected that position from a *trans*-acylation process in the subsequent step and furnished the backbone methyleneoxy unit whose methoxy group could be converted into the most suitable leaving group. Treatment of **269** with the desired acid salt in DMF gave **270,** whose acetolysis gave **271,** which converted it to the bromomethylester **272** (88JMC144).

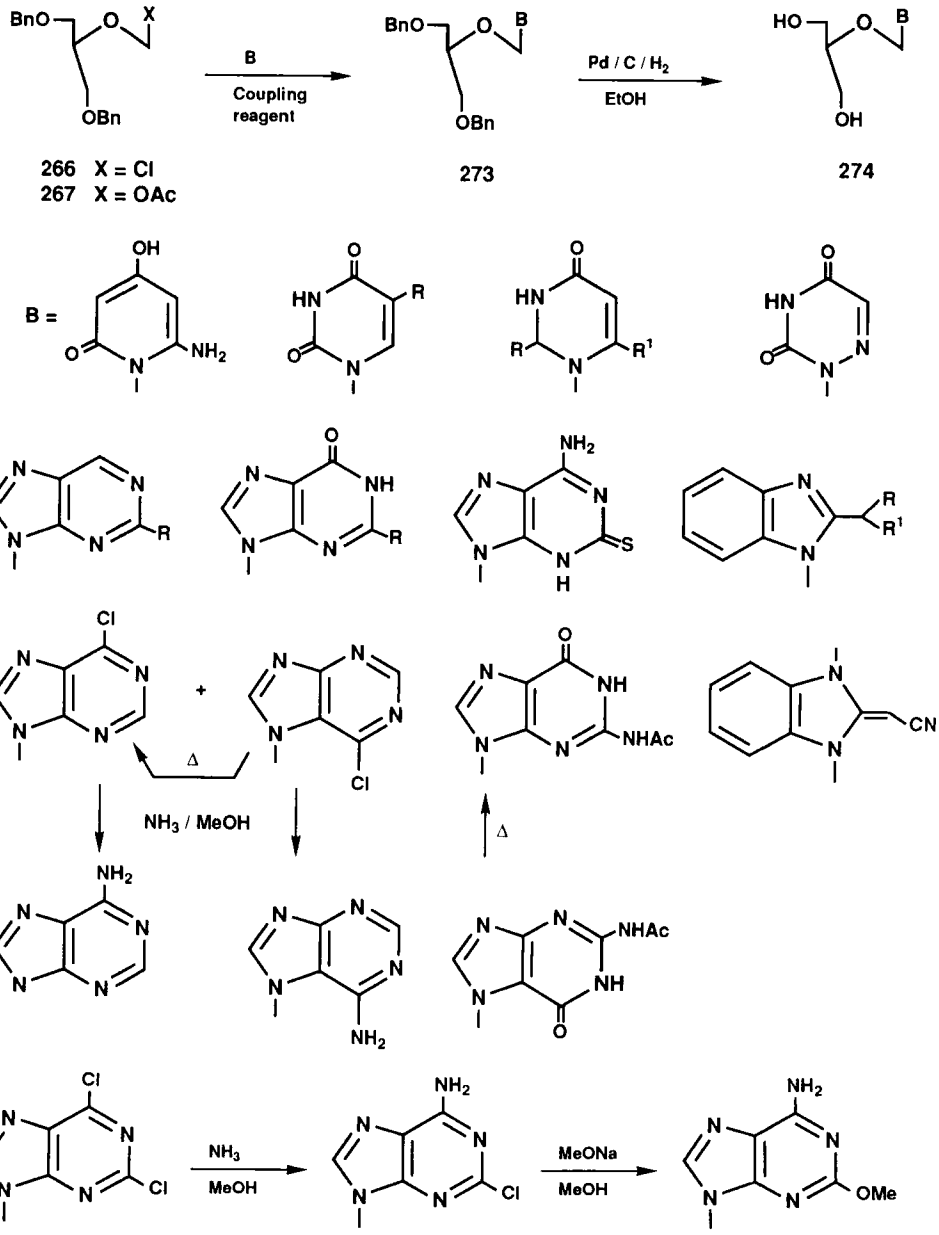
The synthesis was started by condensing the persilylated base with chloromethylether **266** (79JMC21; 82CJC3005; 84CJC16; 85JMC358, 85JMC971, 85USP4508898; 87MI4; 88MI2; 89MI8; 90GEP3906357). Both mercuric cyanide and tetra-*n*-butylammonium iodide (TBAI) were frequently used as catalysts in the coupling reactions. The latter catalyst has the advantages that it is less toxic, is required in smaller quantities, and involves reactions that are generally easier to manipulate during workup. Lithium bromide/TFA/MeCN was also used (88MI2). In the case of triazine derivatives, in addition to the major product, a minor quantity of the 4-alkylated isomer was obtained (91MI5). Direct or phase catalytic hydrogenation of **273** gave **274,** except in the presence of a halogen or nitro group when boron trichloride was used (84CJC16, 84CJC241; 85JMC358, 85JMC971; 87MI2; 93MI1). Attempted debenzylation with BBr_3 gave a 2-methoxymethyl derivative because of complex formation between BBr_3 and the C-2 oxygen. Nucleophilic substitution may have occurred at C-1′ ($N-CH_2-O$) when the complex was quenched by the addition of MeOH (91MI5). However, the chlorine atom in position 6 of 6-chloro-Pu and 6-chloro-Gu could be hydrogenolyzed without any significant loss of the benzyl groups (84-CJC241).

In the case of purine derivatives, the N-7 isomers were obtained, in addition to the N-9 isomers; the N-7 isomers rearranged to the N-9 on



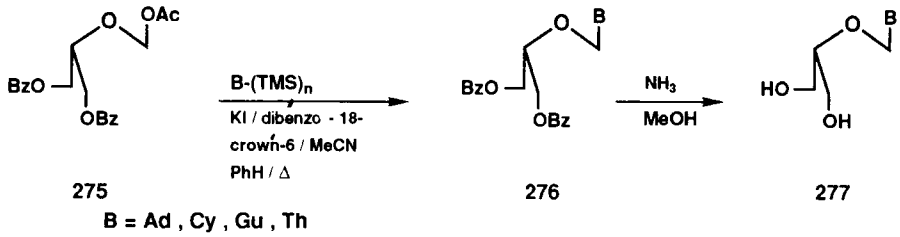
SCHEME 55

heating (84CJC2702). The 6-chloropurines could be converted to the corresponding methoxy or hydroxy derivatives by NaOH/MeOH/H_2O at room temperature and on heating, respectively. The 2-amino-6-chloropurines were converted to the 2-amino-6-methoxypurines and to the guanine analogs by reaction with NaOMe and NaOH/MeOH/H_2O, respectively (84CJC2702). In 2,6-dichloropurine, substitution of the 6-chlorine atom takes place preferentially, by which means another substituent can be introduced later at the 2-position [86IJC(B)823].



Coupling reagent
HMDS / $(CH_3)_2SO_4$ / Bu_4NI / CH_2Cl_2
HMDS / $(CH_3)_2SO_4$ / $Hg(CN)_2$ / PhH
HMDS / $(CH_3)_2SO_4$ / CSI_2 / MeCN
LiBr / TFA / MeCN ; Et_3N / DMF.

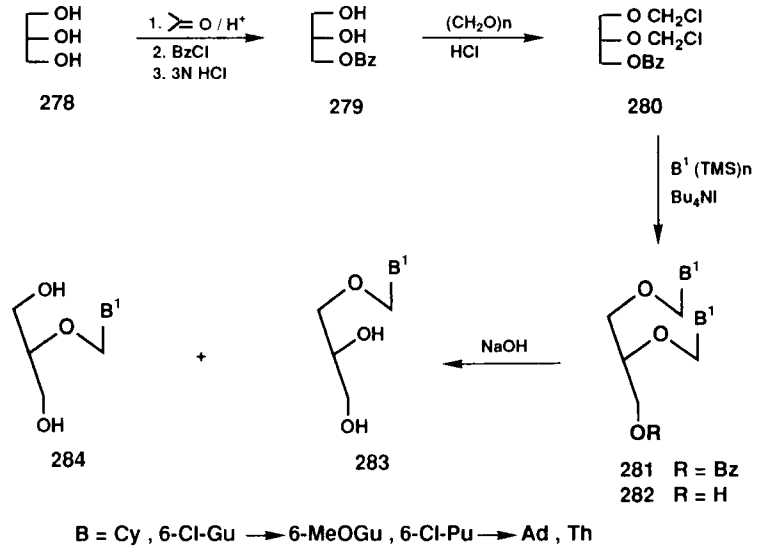
SCHEME 56



SCHEME 57

The synthesis of chiral acyclic nucleosides **276** utilizes the readily available protected acetoxymethyl ether of glycerol **275,** which reacted with silylated nucleobases under phase transfer conditions using dibenzo-18-crown-6 to give N-9 purinyl and N-1 pyrimidinyl acyclonucleosides. Removal of the benzoyl groups by methanolic ammonia gave **277** (88JMC144; 89TL6165).

The bis-chloromethyl ether **280** could also be used for alkylation. Thus, isopropylidenation of glycerol (**278**) followed by benzoylation and deisopropylidenation gave **279,** whose chloromethylation gave **280.** Coupling of the latter with silyl derivatives of bases gave **281,** whose deprotection gave **282,** whereas the use of sodium hydroxide led to a cleavage of one of the methyl ether linkages to give **283** and **284.** The former belongs to nucleoside analogs of type 2.2. Mixed derivatives of **282** were also prepared (86MI2).



SCHEME 58

Another preparation of analogs **287** was by reacting the purine bases with acetal **286** prepared from **285** (92GEP4020481).

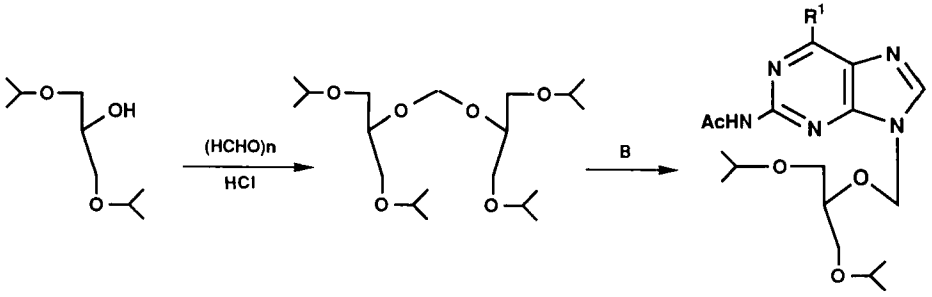
The synthesis could be achieved via a transpurination process by reaction of tetraacetylguanosine **288** with the acetoxymethyl ether **271** using chlorobenzene as a solvent, or with 2-(acetoxymethoxy)-1,3-dibenzyloxypropane (**267**) by fusion to give a separable 9- and 7-isomeric mixture of **289** and **290** (82BBR1716; 89MI5). Heating **290** gave a mixture of **290** and **289.** The reaction of **267** with diacetylguanine gave a similar mixture (83JMC759). The tetraacetyladenosine did not undergo such a transpurination process.

2. *Modification on the Heterocyclic Rings*

Some modifications on the heterocyclic rings are shown in Scheme 56, in particular the use of 6-chloropurine in coupling reactions, followed by substitution of the chlorine by an amino group. Moreover, the preferential substitution of one of the chlorine atoms in 2,6-dichloropurines introduces two different substituents at these two positions.

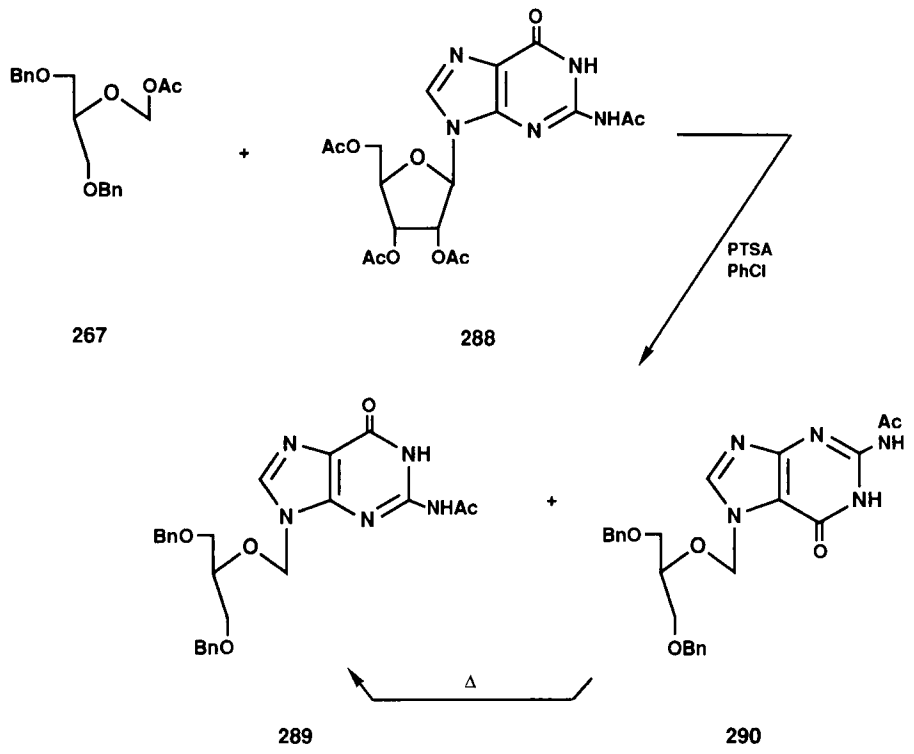
Because of the susceptibility of cytidine derivatives to overreduction on hydrogenolysis of the benzyl ether groups, acyclic analogs were prepared from the uridine analogs by acetylation (Ac_2O/Py) to give **291;** P_4S_{10} treatment gave **294,** whose reaction with NH_3/MeOH gave **296.** In contrast, the fluorocytidine **297** was prepared from **292** via **295** by phosphorodichloridate and triazole followed by ammonia. Bromination (Br_2/Ac_2O/AcOH) of **291** gave **293,** which could be deacetylated with NH_3/MeOH (85JMC358).

The synthesis of the 5-allyl and 5-*n*-propyl derivatives used organopalladium intermediates. The uracil derivative **299** first was treated with mercuric acetate, then was condensed with allyl chloride in the presence of Li_2PdCl_4 to give the 5-allyl derivatives **300** whose reduction gave **301.** Treatment of

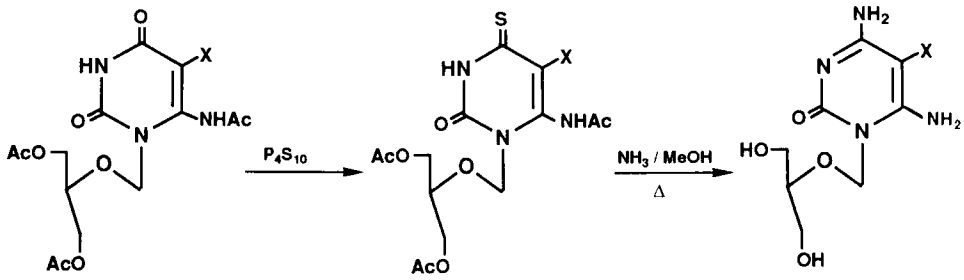


285 286 287

SCHEME 59



SCHEME 60



291 X = H
292 X = F
293 X = Br

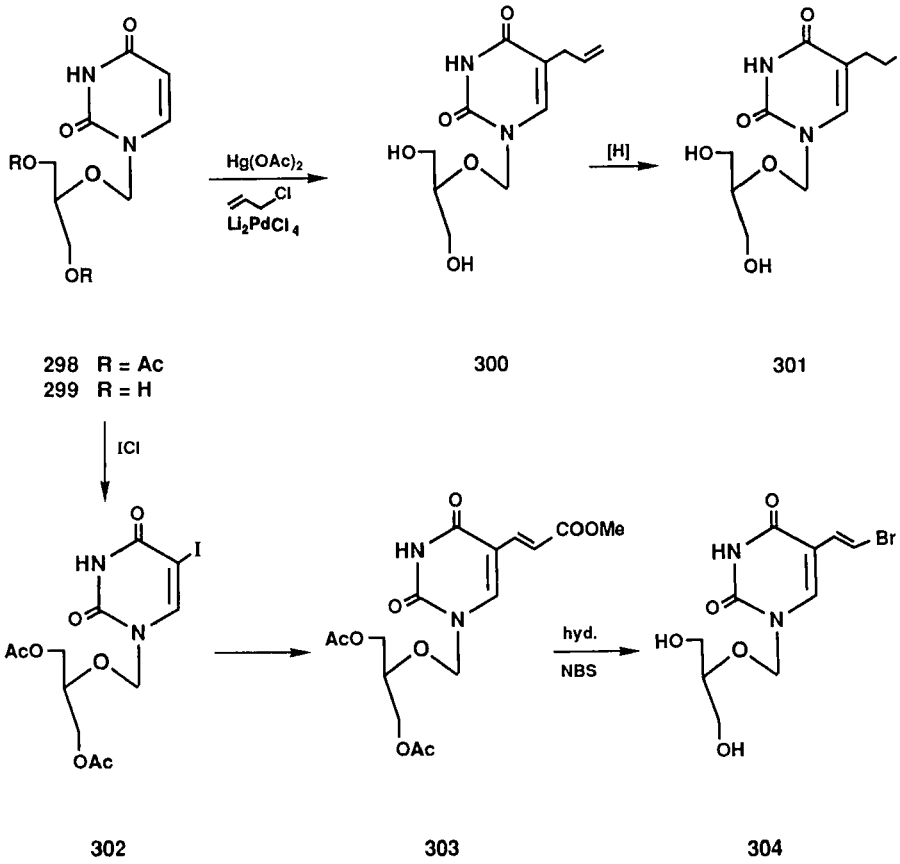
294 X = H
295 X = F

296 X = H
297 X = F

SCHEME 61

298 with iodine monochloride led to the 5-iodo derivative **302.** Compound **302** also served as the starting point for the introduction of the bromovinyl side chain at C-5 by the conversion of the 5-iodo to the 5-methyl propenoate **303.** The ester groups in **303** were hydrolyzed, and the bromine atom was introduced using *N*-bromosuccinimide to give **304** (84CJC16). None of the compounds tested showed significant activity.

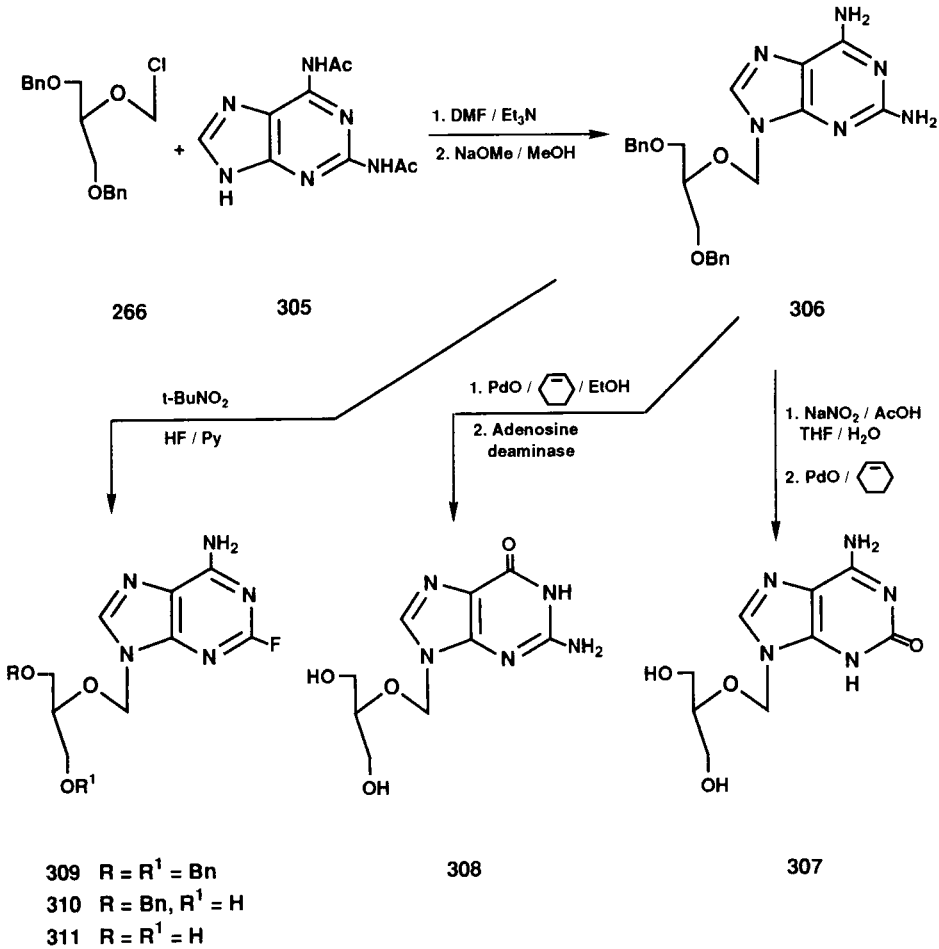
Coupling base **305** with **266** gave **306.** Selective replacement of the amino group by halogens via treatment of **306** with *t*-butyl nitrite in 60% HF/pyridine gave the 2-fluoro derivative. The reaction conditions also resulted in the partial loss of benzyl groups to form **309–311.** The 2-amino group in **306** could also be selectively diazotized to an oxygen function, giving rise to the isoguanine structure. Removal of the benzyl groups gave the



SCHEME 62

isoguanine derivative **307,** which is isomeric with BIOLF-62. The 2,6-diaminopurine derivative was treated with an excess of adenosine deaminase, which was quantitatively converted into BIOLF-62 (**308**) (84CJC241). The dimethylaminomethylene acyclonucleosides were prepared by reactions of the amine group with *N,N*-dimethylformamide dimethyl acetal in DMF/MeOH (85MI5).

The synthesis of the 7-deazapurine and 5-aza-7-deazapurine analogs of DHPG were prepared by the alkylation of the respective heterocycles **312** and **316** with **266** and **267,** respectively. A mixture resulting from the



309 R = R^1 = Bn
310 R = Bn, R^1 = H
311 R = R^1 = H

308 **307**

SCHEME 63

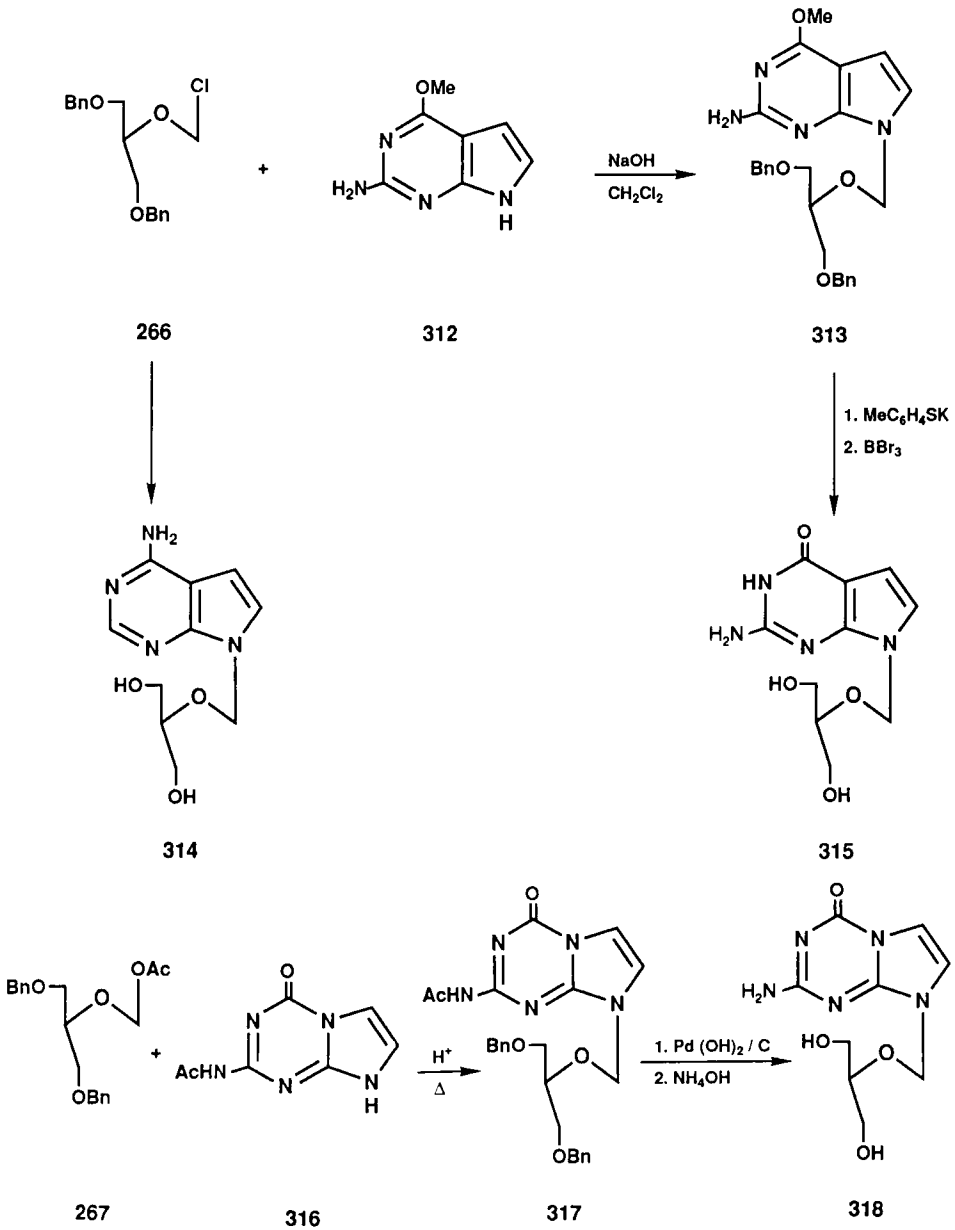
alkylation of N-3 and N-9 was obtained. Deprotection of **313** and **317** gave **315** in the former case, whereas in the latter case the product **318** was contaminated with the dihydro derivative; isolation was done by silylation, purification by chromatography, and then desilylation (85JHC1137). The 4-substituted analogs **314** were prepared via the 4-chloro derivative and then amination (89MI1). Compounds **315** were inactive against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) in cell culture, whereas **318** had moderate antiviral activity. Compound **314** showed poor antiviral activity against Cox B6 virus.

The analogs of tubercidin, toyocamycin, and sangivamycin were prepared by treatment of the sodium salt of 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidines with **266,** followed by debromination, and then debenzylation with BCl_3. Conventional functional group transformation of the cyano group to $CONH_2$, $CSNH_2$, and $C(NOH)NH_2$ was also done. 4-Chloro-2-methylthiopyrrolo[2,3-*d*]pyrimidine was aminated, desulfurized, and then debenzylated to give the tubercidin analog (89JMC402).

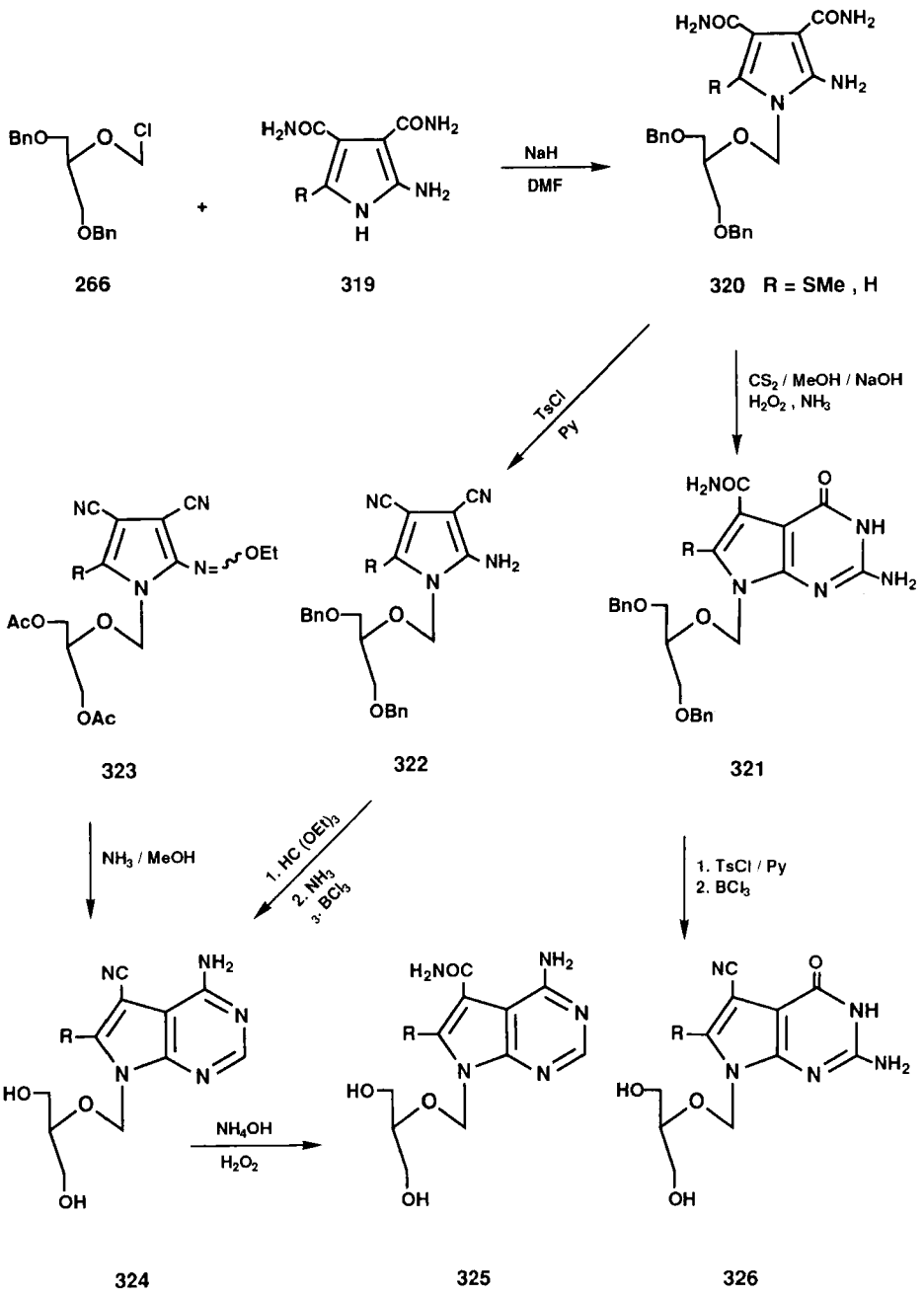
The synthesis of acyclic 7-deazapurine nucleosides involving a pyrrole nucleoside intermediate as a common synthon to both the 7-deazaadenosine and the 7-deazaguanosine analogs was achieved. The construction of these key intermediates (**320**) involves the treatment of the Na salt of the pyrrole derivative **319** with the electrophile **266** in DMF. Desulfurization of **320** (R = SMe) using Raney nickel afforded **320** (R = H). Dehydration of the carboxamide functionalities of **320** gave the corresponding dinitrile **322.** Treatment of **320** with carbon disulfide followed by direct oxidation and then treatment with ammonia afforded **321.** The amide was transformed to the nitrile and then deprotected to give **326.** The 7-deazaadenine analogs were prepared by reacting the aminopyrrole **322** with triethyl *ortho*-formate followed by displacement of the ethoxy group by ammonia and subsequent cyclization and deprotection to afford the 7-deazapurine ring system **324,** which could also be prepared from **323.** The nitrile was transformed to the amide **325.** The 7-deazaadenine analogs show activity against HIV (90JMC2162; 92MI7).

The synthesis of 8-azapurine analog **330** was done by the chloroalkylation of the alcohols **265** followed by replacement of chlorine with azide to give **327.** Cyclization with cyanoacetamide gave the 1,2,3-triazoline **328.** Deprotection formed **329,** and cyclization of **328** with ethyl formate and deprotection gave **330** (88S879). The same strategy was used to prepare analogs of types 2.2 and 3.1.

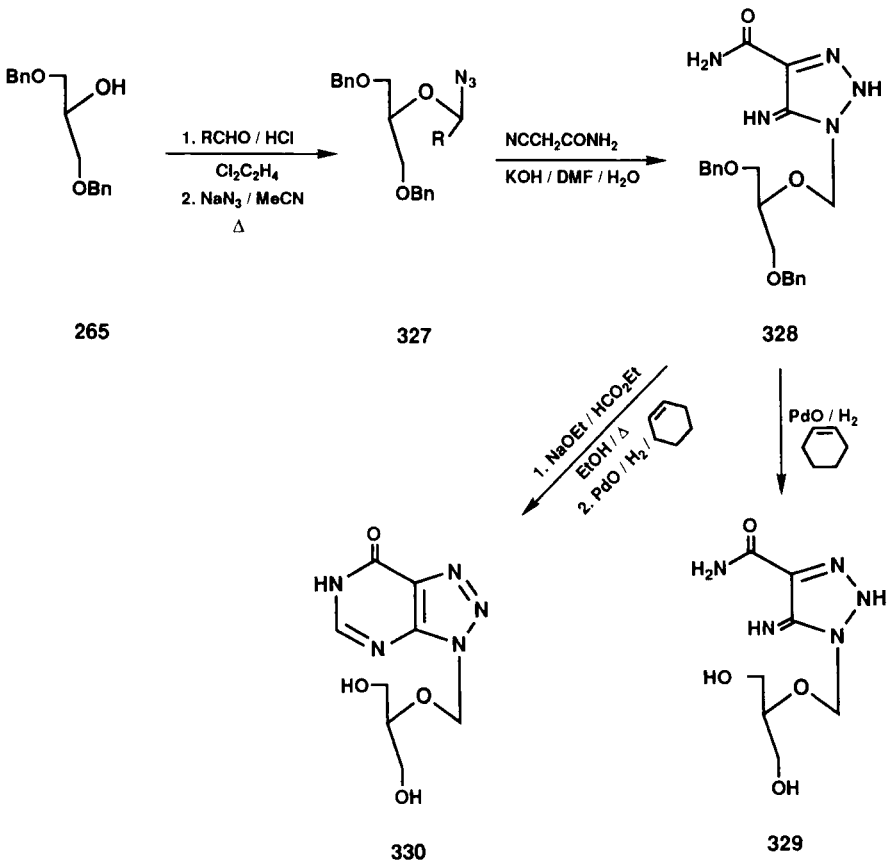
Analogs with a sulfur instead of an oxygen atom in the side chain were also prepared. Thus, the starting synthon **332** was prepared from **265** via **331** in four steps. Alkylation of **332** with the silyl derivative of 2-amino-6-chloro-9*H*-purine gave a mixture of **334** and its N-7 isomer that could be


BnO
Cl
OBn
OMe
N
H2N
N
N
H
NaOH
CH2Cl2
OMe
N
H2N
N
N
BnO
O
OBn
266
312
313
1. MeC6H4SK
2. BBr3
NH2
N
N
N
HO
O
OH
HN
O
H2N
N
N
HO
O
OH
314
315
BnO
OAc
O
OBn
AcHN
O
N
N
N
H
H+
Δ
AcHN
O
N
N
N
BnO
O
OBn
1. Pd (OH)2 / C
2. NH4OH
H2N
O
N
N
N
HO
O
OH
267
316
317
318

SCHEME 64


BnO
O
Cl
OBn
266
+
H2NOC
CONH2
R
N
H
NH2
319
NaH
DMF
320 R = SMe , H
TsCl
Py
CS2 / MeOH / NaOH
H2O2 , NH3
NC
CN
N=OEt
AcO
OAc
323
322
321
NH3 / MeOH
1. HC(OEt)3
2. NH3
3. BCl3
1. TsCl / Py
2. BCl3
HO
OH
NH4OH
H2O2
324
325
326

SCHEME 65



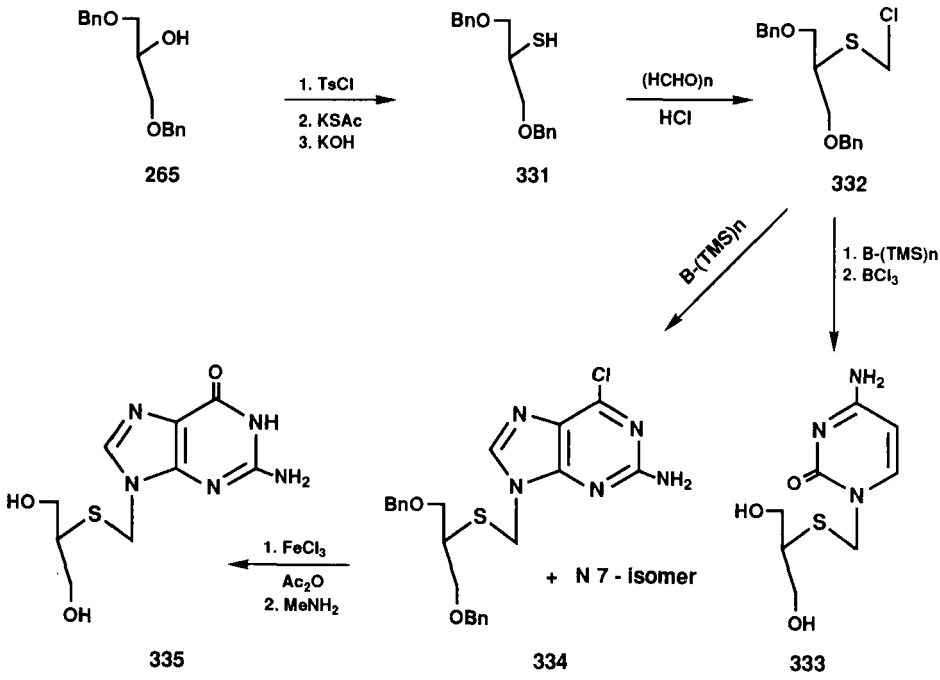
265 327 328

330 329

SCHEME 66

separated, whereas the use of the respective guanine led to a mixture that could not be isolated. Acetolysis of **334** with ferric chloride in Ac_2O and then deacetylation gave **335.** The cytosine analog **333** was similarly prepared from **332** by reaction with a fivefold excess of the cytosine followed by debenzylation to give **333** (89MI3). Tautomeric purine derivatives were prepared (80USP4199574; 85EUP145207; 90EUP349243). The introduction of an amino group at the 8-position was done by bromination with NBS, hydrazinolysis, and reduction. Guanine analogs were also reported.

The influence of these acyclic nucleosides on the growth of L5178 mouse lymphoma cells and antiherpes activity has been a subject of great interest (83MI1, 83MI2; 84MI2, 84MI3; 85MI3; 90EUP375329, 90USP4968686). The



SCHEME 67

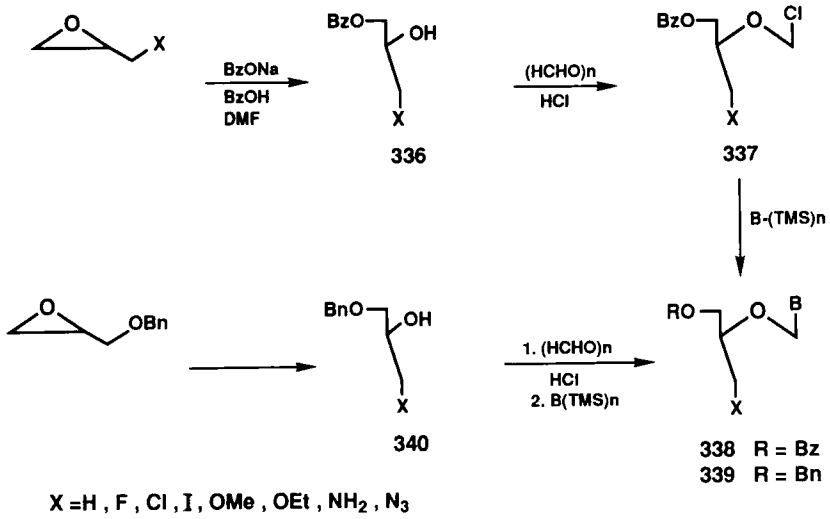
Gu analog (DHPG BIOLF-62) has shown remarkable activity against herpes virus (82CJC3005, 82MI3; 83MI3; 84CJC16; 85EUP161955; 85MI1). *In vitro* studies indicate that DHPG is a potent and broad-acting (herpes simplex virus types 1 and 2, cytomegalovirus, and Epstein–Barr virus) antiherpetic agent. *In vivo* studies indicate its lack of toxicity and its superiority over acyclovir (83JMC759). The 6-H_2-Pu is active against CMV. The 2-amino-6-isopropyl Pu and its esters with long-chain acyl groups were prepared as prodrugs (89AUP388734). The 6-Cl-Gu derivative is active against HSV-1 (84CJC241) and showed high activity against Coxsackievirus 3 in *in vivo* testing in mice. The uracil analogs show little activity against herpes viruses (84CJC16). Pyrimidine analogs inhibited the proliferation of P388 mouse leukemia [88JAP(K)63/060929]. None of the triazine derivatives were active against HSV-1 and HSV-2 or inhibited toxic effects in uninfected HFF cells (93MI1). Antiviral testing showed that a cytosine analog was equivalent to the guanine analog in potency against human cytomegalovirus and Epstein–Barr virus (88JMC144). The structure–activity relations among selected purine and pyrimidine nucleosides have been studied (88AF1545).

The acyclic analogs of tubercidin, toyocamycin, and sangivamycin had only slight-growth inhibitory activity against L_{1210} murine leukemic cells. The corresponding derivative with $CSNH_2$ was more potent in inhibiting HCMV but not HSV-1 (89JMC402).

Virucidal activity of an imidazole analog against entero- and coronavirus is increased by the addition of hydroxyalkyl groups in the side chain (88DOK58, 88KFZ833). Neither this analog **333** nor **335** had significant *in vitro* activity against human cytomegalovirus (89MI3).

3. *Deoxyhalogeno Analogs*

Analogs of DHPG with one of the alcohol functionalities on the side chain replaced by another functionality were also prepared. The chlorodeoxy precursors were prepared from epichlorohydrin by ring opening to give **336,** which chloromethylated to give **337** (X = Cl). Alternatively, ring opening of benzyloxy epoxide gave **340,** whose chloromethylation and coupling gave **339** (86JMC1384; 91MI6). Similarly, the chloro analogs **339** were prepared by reacting bis(trimethylsilyl)adenine and tris(trimethylsilyl) guanine, and bis(trimethylsilyl)uracil after treatment with one equivalent of Bu_4NF, which presumably removes the Me_3Si from their N-9 or O-2, with 1-chloro-3-benzyloxy-2-propoxymethyl chloride and deblocking (89MI6; 90HCA912). Reaction with 2,9-diacetylguanine and then deprotection gave **338** (86JMC1384).



SCHEME 68

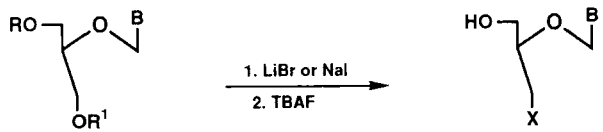
Partial protection of DHPG as bis(monomethoxytrityl) derivative followed by mesylation gave **341,** whose displacement with a variety of nucleophiles and deprotection gave **342** (86JMC1384; 89MI6). An *in vitro* assay against HSV-1 showed that all compounds were less active than DHPG, though the fluoro analog was a good substrate for the viral thymidine kinase.

The optically pure fluoro analogs of thymine and adenine were synthesized (93T713). The (2*S*)-1-fluoro-3-(*R*)-[(4-methylphenyl) sulfinyl]-2-propanol **343** was used as a starting material, which was converted to methoxymethyl ether **344.** Treatment with trifluoroacetic anhydride and 2,4,6-trimethylpyridine in acetonitrile gave, via a Pummerer rearrangement, a geminal trifluoroacetyloxy-tolylthio intermediate as a masked aldehyde, which hydrolyzed *in situ* with mercuric chloride. Reduction with sodium borohydride followed by benzylation gave **345.** Hydrolysis of the methoxymethylene group gave **346,** whose chloromethylation gave **347.** Replacement of the chlorine with thymine gave **348,** which deprotected to **351.** The reaction with 6-chloropurine gave 9-alkylated isomer **349** in addition to a minor amount of N-7 isomer. The major isomer was transformed to the adenine derivative, which deprotected to give **350** (93T713). The synthesis of enantiomerically pure 1′,2′-*seco*-nucleosides was almost similarly achieved (92G493).

The dichlorodideoxy derivative **353** was prepared by reacting **352** with trimethylsilylated thymine in presence of n-Bu_4NI. Compound **353** was treated with potassium acetate in DMF to give the acetoxy derivative, which was then treated with methanolic ammonia to give **354** in low yield (89MI4).

4. *Deoxyazido and Deoxyamino Analogs*

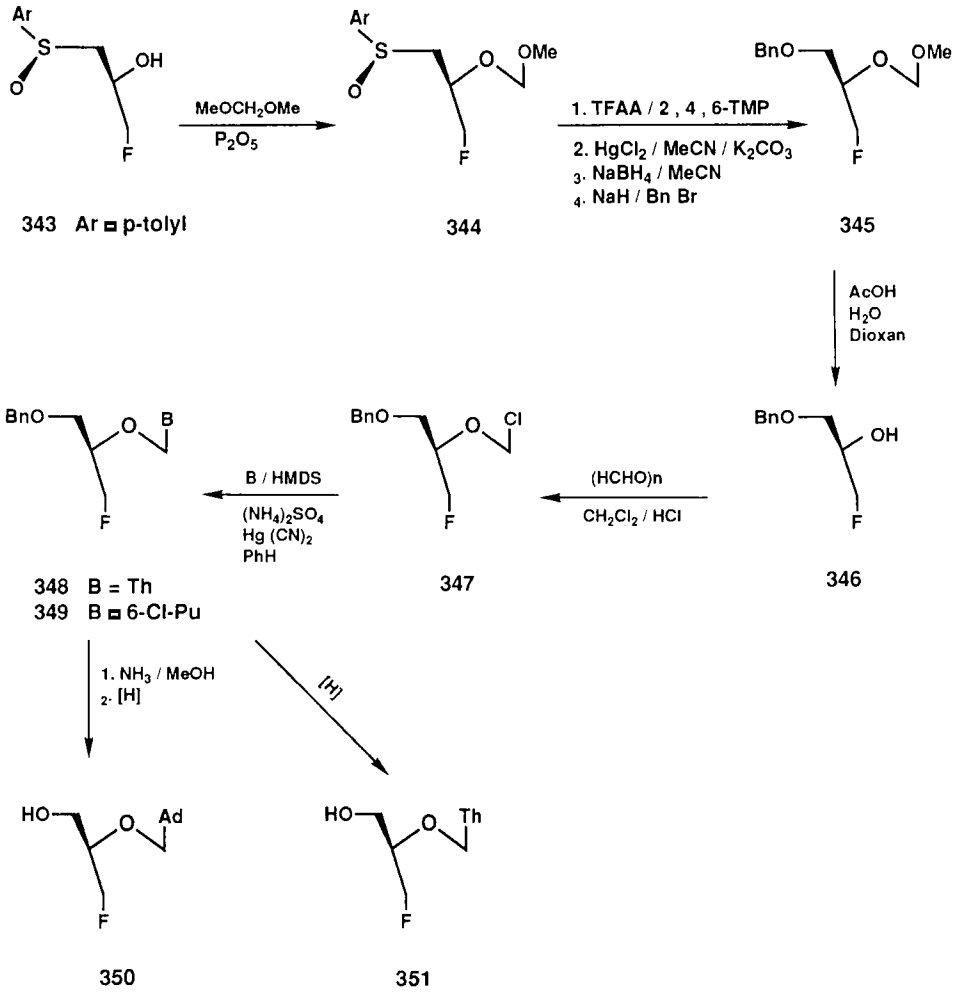
The chiral glycerol derivative **355** was prepared by lipase-catalyzed asymmetric *trans*-esterification. Tosylation of **355** followed by hydrolysis gave **356.** Hydrogenolysis of **356** gave 3-tosyloxy-1,2-propanediol (**357**). After



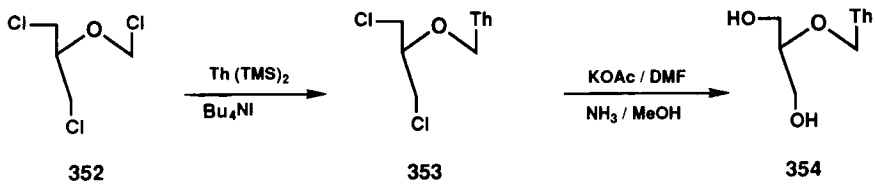
341 **342**

R = DMBS , R^1 = Ms , B = Ad
R = MTr , R^1 = Ts , B = Gu MTr

SCHEME 69



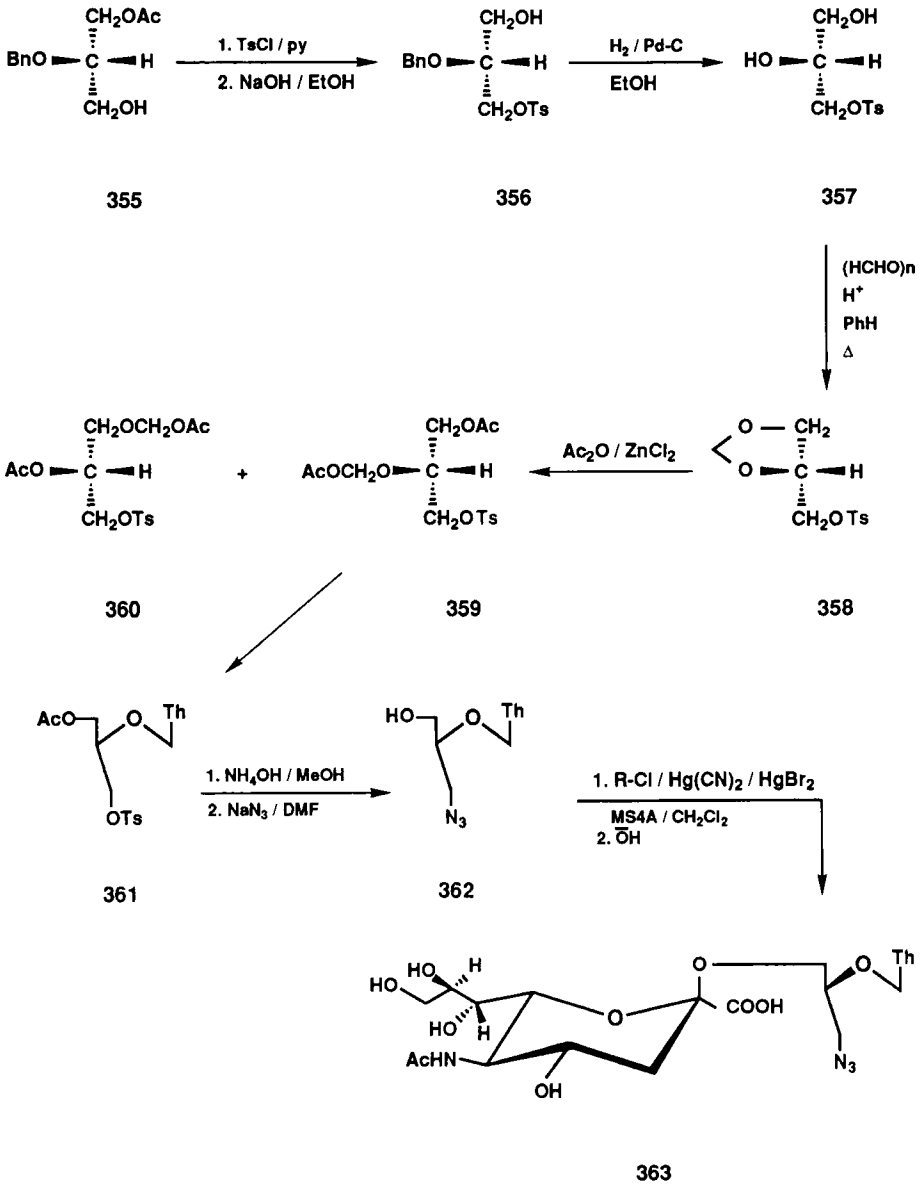
SCHEME 70



SCHEME 71

formylation of **357** with trioxane, the resulting **358** was acetylated with acetic anhydride and $ZnCl_2$ to give a mixture of the acetoxymethyl ethers **359** and **360.** The former was treated with bis(trimethylsilyl) thymine in presence of a Lewis acid to give the acyclonucleoside **361.** Acyclo AZT (**362**) was synthesized from **361** by deacetylation followed by treatment with sodium azide in DMF. Treatment of acyclo AZT with the sugar chloride in presence of mercuric cyanide and mercuric bromide gave the respective α- and β-glycosides, whose deacetylation afforded the α- and β-anomers of *N*-acetyl-D-neuraminyl-(2→2)-(*S*)-1-{[2-azido-1-(hydroxymethyl)ethoxy]-methyl}thymine (Neu5Ac-acyclo AZT) **363** [90CPB836, 90JAP(K)02/009870].

The optically active compound 1-*O*-benzyl-D-glycerol (**364**), which was prepared from D-mannitol, was used as the common starting material for the synthesis of the key chiral intermediates, (*R*)- and (*S*)-1-benzyloxy-3-azido-2-propanol (**368, 370**). Partial tosylation of **364** gave the corresponding 3-*p*-toluenesulfonate **371,** which was further reacted with lithium azide to furnish the (R)-azido enantiomer **370.** On the other hand, tosylation of **364** gave the 2,3-di-*O*-*p*-toluenesulfonate **365,** whose treatment with sodium benzoate in DMF gave the benzoate ester **366,** selectively. Treatment of compound **366** with sodium methoxide resulted in an internal S_N2 displacement reaction, yielding (*R*)-benzyl-2,3-epoxypropyl ether **367** with inversion of configuration at carbon-2. Ring opening of the epoxide **367** with lithium azide afforded the other desired intermediate (*S*)-azido enantiomer **368.** Treatment of the chiral alcohols **368** and **370** with paraformaldehyde and anhydrous hydrogen chloride gas afforded the corresponding chloromethyl ethers **369** and **372.** Each was then coupled with bis(trimethylsilyl)-5-benzyluracil in refluxing toluene under anhydrous conditions to yield the protected azido acyclonucleosides **374** and **373,** respectively. Hydrogenation gave the corresponding amino derivatives. The removal of the benzyl protecting group could not be achieved by the same catalytic hydrogenation conditions. However, by converting the amino derivatives first to their corresponding hydrochloric acid salts, and then following the same reduction conditions just mentioned, the respective final deblocked acyclicnucleosides **375** and **376** were obtained. The (*R*) and (*S*) enantiomers have the same affinity for binding to uridine phosphorylase and have marked high water solubility (90MI3). Similarly, thymine, uracil, 6-azathymine, 6-azauracil, 5-phenyl-6-azauracil, or 5-benzyl-6-azauracil were prepared; their debenzylation with boron trichloride in dichloromethane afforded the desired products of azido-acyclic nucleosides **377** (91MI6). None of them exhibited significant antiviral activity against human immunodeficiency virus and herpes simplex virus.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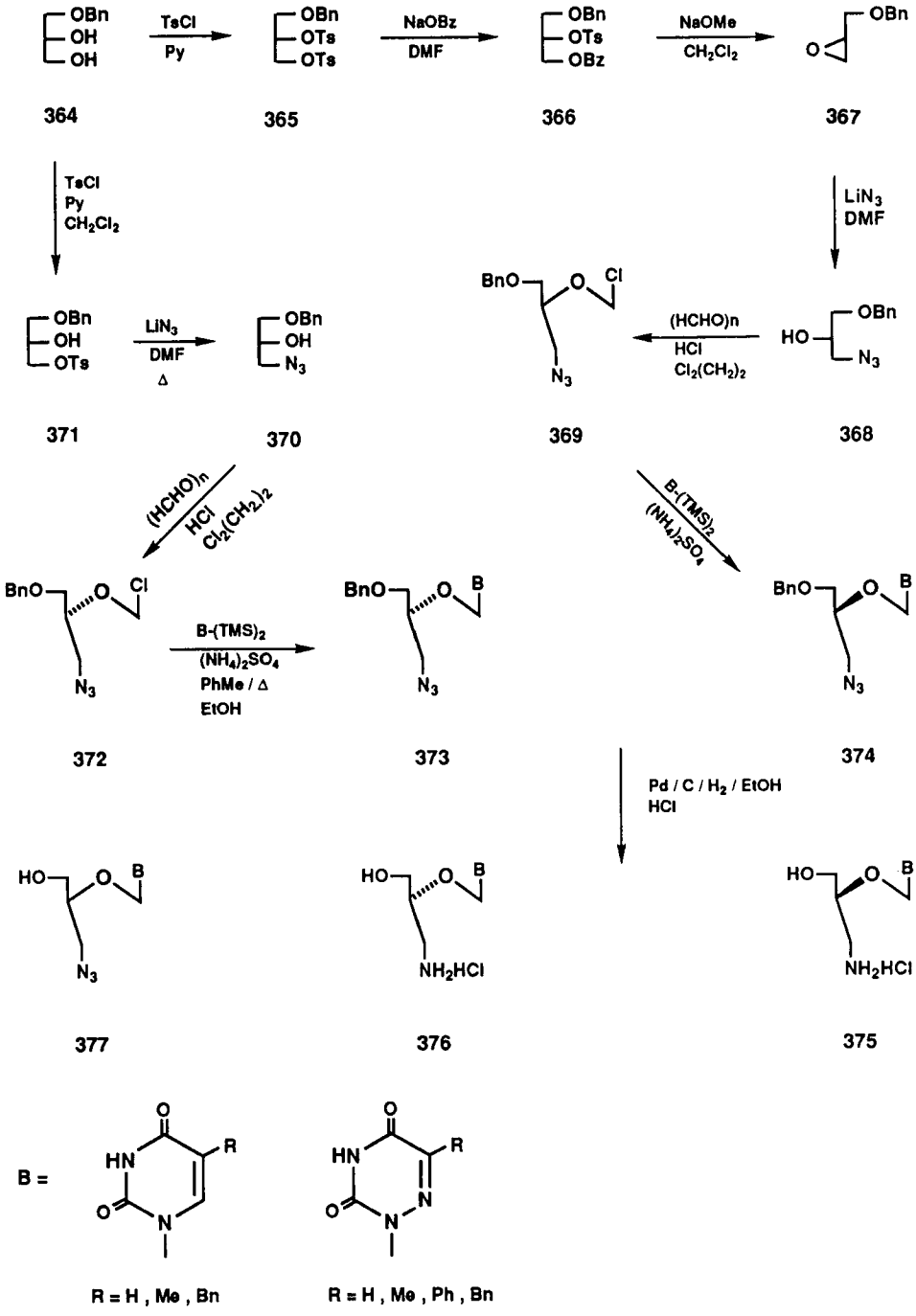
BnO
C
H
CH2OH
1. TsCl / py
2. NaOH / EtOH
CH2OH
BnO
C
H
CH2OTs
H2 / Pd-C
EtOH
CH2OH
HO
C
H
CH2OTs
355
356
357
(HCHO)n
H+
PhH
Δ
CH2OCH2OAc
AcO
C
H
CH2OTs
+
CH2OAc
AcOCH2O
C
H
CH2OTs
Ac2O / ZnCl2
O — CH2
O
C
H
CH2OTs
360
359
358
AcO
O
Th
OTs
1. NH4OH / MeOH
2. NaN3 / DMF
HO
O
Th
N3
1. R-Cl / Hg(CN)2 / HgBr2
MS4A / CH2Cl2
2. OH
361
362
HO
H
HO
HO
H
AcHN
OH
O
O
COOH
O
Th
N3
363

SCHEME 72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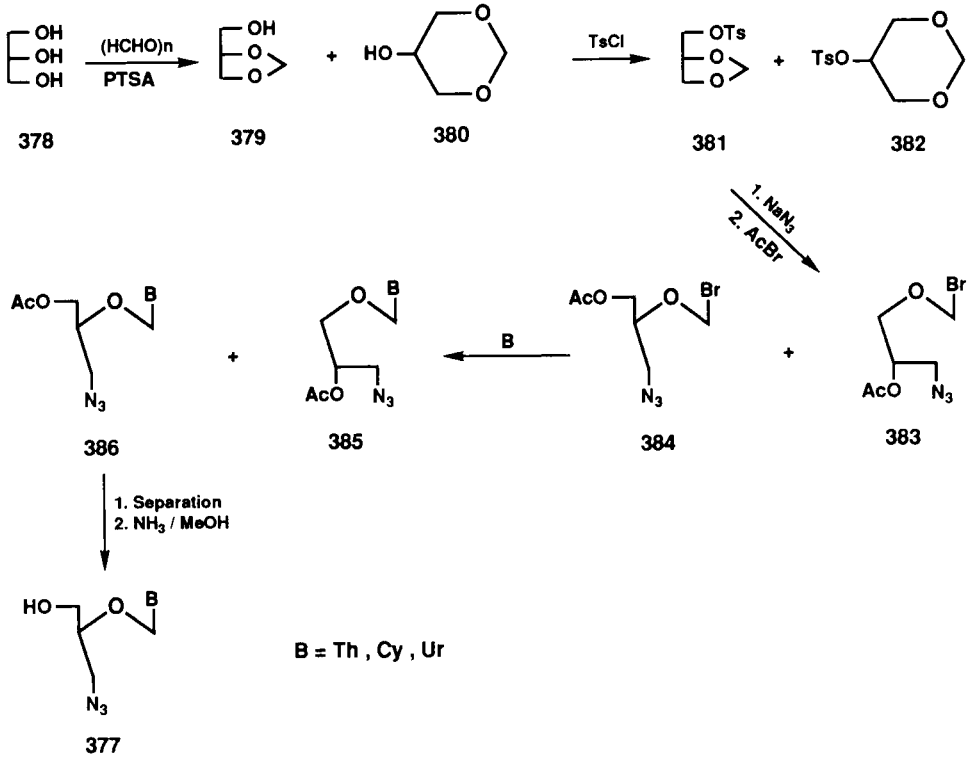
OH
TsCl
Py
OBn
OTs
OTs
NaOBz
DMF
OBn
OTs
OBz
NaOMe
CH2Cl2
OBn
O
364
365
366
367
TsCl
Py
CH2Cl2
LiN3
DMF
OBn
OH
OTs
LiN3
DMF
Δ
OBn
OH
N3
BnO
O
Cl
N3
(HCHO)n
HCl
Cl2(CH2)2
HO
OBn
N3
371
370
369
368
(HCHO)n
HCl
Cl2(CH2)2
B-(TMS)2
(NH4)2SO4
BnO
O
Cl
N3
B-(TMS)2
(NH4)2SO4
PhMe / Δ
EtOH
BnO
O
B
N3
BnO
O
B
N3
372
373
374
Pd / C / H2 / EtOH
HCl
HO
O
B
N3
HO
O
B
NH2HCl
HO
O
B
NH2HCl
377
376
375
B =
O
HN
R
O
N
O
HN
R
N
O
N
R = H , Me , Bn
R = H , Me , Ph , Bn

SCHEME 73

A similar approach utilizing (+)-epichlorohydrin was carried out. Coupling with silylated thymine in the presence of TMSOTf, deprotection, and catalytic hydrogenation gave the amine. *O*-Thexyldimethylsilylation of the azide followed by reduction and then reaction with cyanogen bromide gave the *N*-cyano derivative and with 2,4,5-trichlorophenylformate in DMF containing ethyldiisopropylamine gave the *N*-formyl derivative. Desilylation was done with BU_4NF (91TL1447).

The reaction of glycerol **378** with *para*-formaldehyde catalyzed by *p*-toluenesulfonic acid has been reported to give a mixture of glycerol formal **379** and **380** that upon tosylation and then separation gave two isomers **381** and **382.** Azide salt was reacted with 3-*O*-tosyl derivative **381** to give 3-azidoglycerol formal and treatment with acetyl bromide resulted in acylative cleavage of the C(2) — O bond to give the two isomers bromomethyl ether acetates **383** and **384.** Their coupling with silylated pyrimidines produced a mixture of **385** and **386,** which were separated by chromatography. Deacetylation of **386** gave **377** (89MI7).



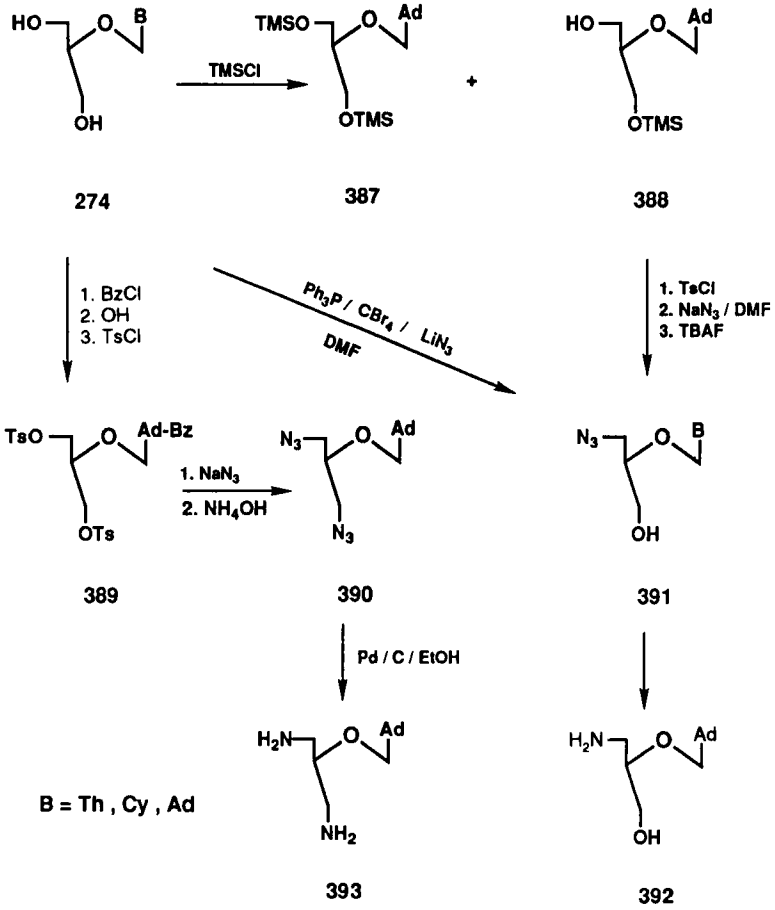
378 **379** **380** **381** **382**

386 **385** **384** **383**

377

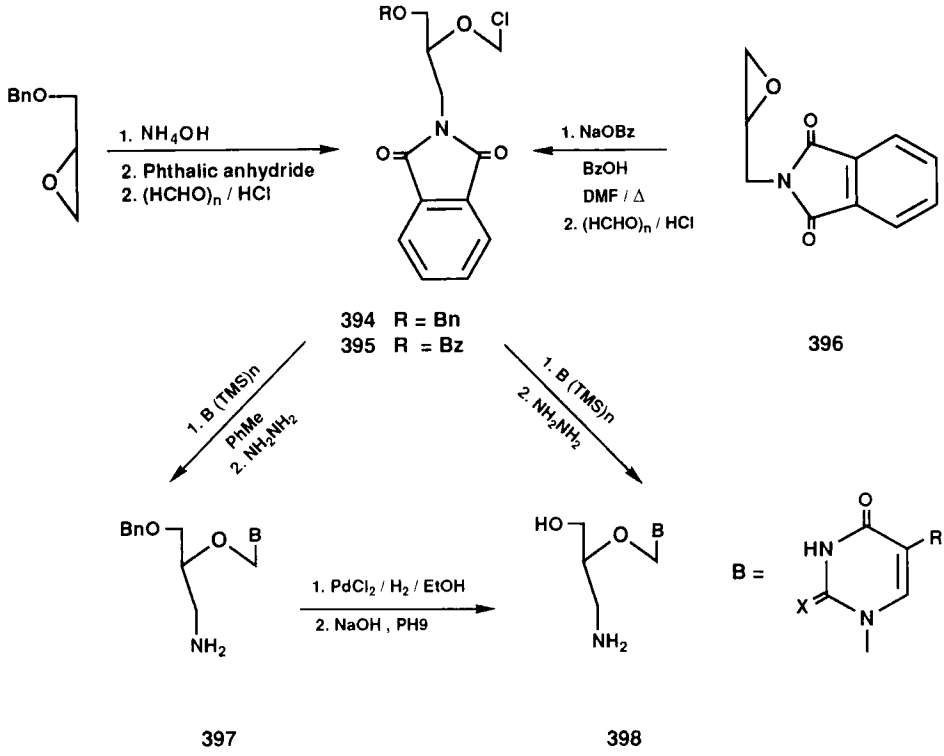
SCHEME 74

Alternatively, the azido functionality was introduced onto an already prepared nucleoside. Thus, silylation of **274** gave **387** and **388.** The hydroxy group in the latter was tosylated, and then displaced with azide ion and deprotected to give **391,** whose reduction gave **392.** The diazide derivative **390** was prepared via the respective ditosylate **389,** whose reduction gave **393** (84CJC241). Treatment of **274** with a combination of triphenylphosphine-carbontetrabromide–lithium azide gave **391.** In the case of an adenine analog, the diazide **390** was found as a by-product (84CJC241). However, the use of carbon tetraiodide led to **391** without by-products [89MI4; 90JAP(K)02/022268]. These compounds have been evaluated for cytotoxicity and inhibition of HIV replication in MT_4, but no activities were detected.



SCHEME 75

The introduction of an amino function into the acyclic sugar moiety started with the treatment of 3-benzyloxypropylene oxide with concentrated aqueous ammonium hydroxide, which then underwent S_N2 substitution to give 1-amino-3-benzyloxy-2-propanol. Further reaction with phthalic anhydride in toluene resulted in the formation of *N*-(3-benzyloxy-2-hydroxypropyl)phthalimide. Chloromethylation by reaction with *para*-formaldehyde and dry HCl in 1,2-dichloroethane yielded (1-benzyloxy-3-phthalimido-2-propoxy)methyl chloride (**394**). Alternatively, reaction of epichlorohydrin with potassium phthalimide gave **396.** It was converted with sodium benzoate in the presence of benzoic acid in DMF, and then treated with 1,3,5-trioxane in presence of HCl to **395.** With **394** and **395,** the persilylated bases were alkylated, and the phthaloyl protecting group was removed with hydrazine in ethanol to form **397** from **394** and **398** from **395.** Deprotection by cyclohexene in ethanol with a catalytic amount of $Pd(OH)_2$ afforded **398** (91MI5). Most showed little toxicity toward HeLa cells and 50% inhibitory levels against HSV-1 (90HCA912).



SCHEME 76

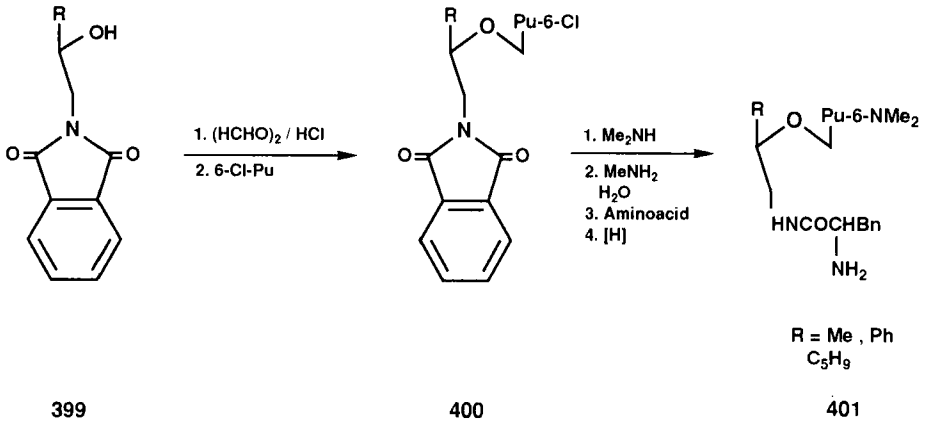
The aminodeoxy analogs were found to be very potent inhibitors of uridine phosphorylase isolated from sarcoma, and they exhibited no apparent cytotoxicity against sarcoma 180 host cells. Furthermore, they have shown excellent water solubility, which is a factor critical for the formulation that often limits the usefulness of a particular compound as a chemotherapeutic agent (85JMC971).

Similarly, the puromycin analogs were prepared from **399** by chloromethylation and coupling with 6-chloropurine to give **400,** which was reacted with dimethylamine, followed by dephthaloylation, coupling with DL-*N*-carbobenzoxyphenylalanine, and then hydrogenolysis to give **401** (85JPS1302).

5. *Branched-Chain Analogs*

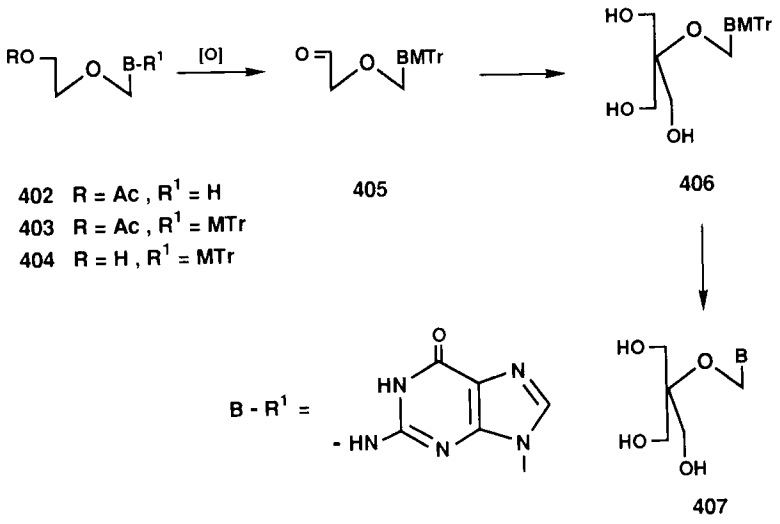
The trihydroxy analog **407** was prepared by acetylation of acyclovir to give **402,** which monomethoxytritylated to **403** and then deacetylated to **404.** Moffatt oxidation of **404** gave **405,** which upon a crossed aldol-Cannizaro reaction gave **406,** whose deprotection gave **407** (86JMC1384).

The starting material, 1,3-dibenzyloxy-2-propanol **265,** is easily oxidized to the ketone **408** using *N*-chlorosuccinimide and dimethyl sulfide. Compound **408** was smoothly converted into the epoxide **409.** The epoxide ring was opened by the attack of benzylate anion at the least hindered site to produce 2-benzyloxymethyl-1,3-dibenzyloxy-2-propanol (**410**), which was activated as the thiomethyl ether system **411** using acetic anhydride in DMSO. The thiomethyl ether is readily activated by iodine, allowing nucleophilic attack at the methylene position. As a result, compound **411** was



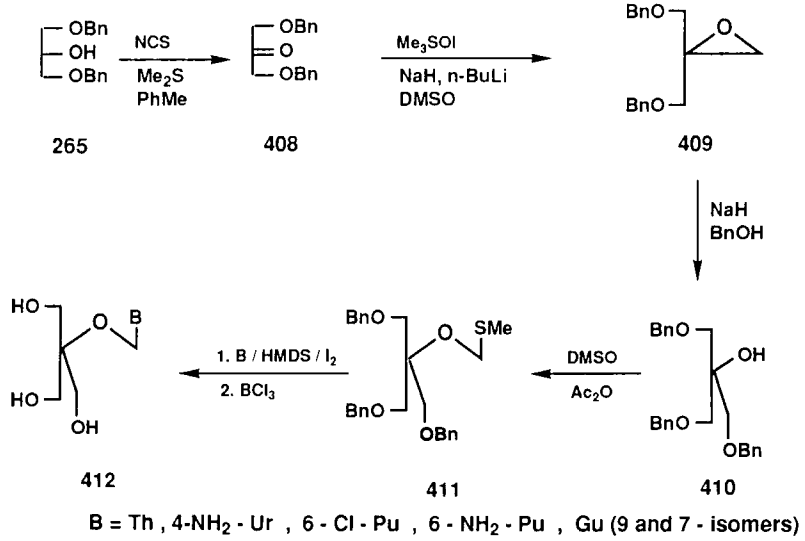
399 400 401

SCHEME 77

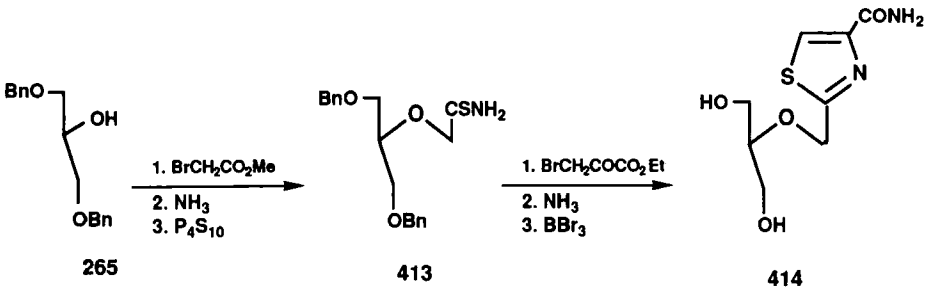


SCHEME 78

coupled to purines and pyrimidines using the silylated base procedure. As usual, the guanine derivative was produced in the lowest yield. The N-7 isomer is produced in significant quantity along with the N-9 isomer. The N-7 isomer crystallizes from solution after removal of the *N*-acetyl group



SCHEME 79



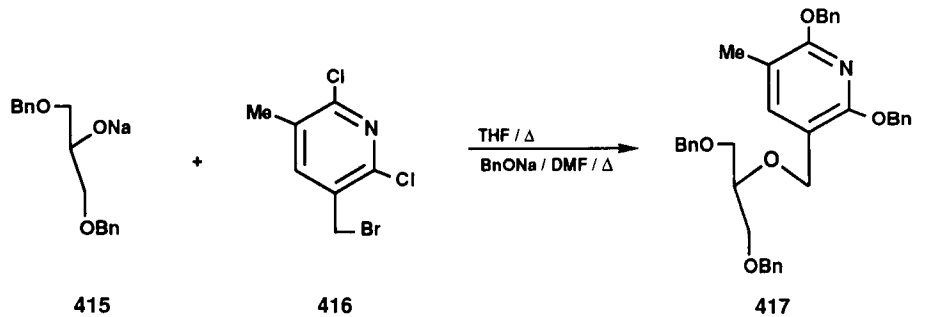
SCHEME 80

from the direct condensation product. The route chosen to the adenine derivative involved 6-chloropurine in the condensation step. Very little of the N-7 isomer is present at the end of the reaction. The chlorine at position 6 is readily displaced by ammonia to give the adenine derivative (84CJC1622; 87BBA127). Only the guanine derivative had an ED-50 of less than 100 μg/ml with HSV-1.

6. *Acyclo-C-nucleoside Analogs*

The *C*-nucleoside analogs of this type of acyclonucleosides were prepared by essentially two methods: sequential *O*-alkylation of **265** with methyl bromoacetate followed by amidation; and sulfurization to give **413,** which cyclized with ethyl bromopyruvate to the thiazole carboxylate, whose amidation and debenzylation gave thiazofurin analog **414** (87H947).

Alternatively, heterocycles carrying a bromomethyl group could be used as alkylating agents to provide the targeted acyclo-*C*-nucleoside analogs. Thus, alkylation of the sodium salt **415** with **416** followed by substitution of the chlorine atoms gave **417** (91T10065).

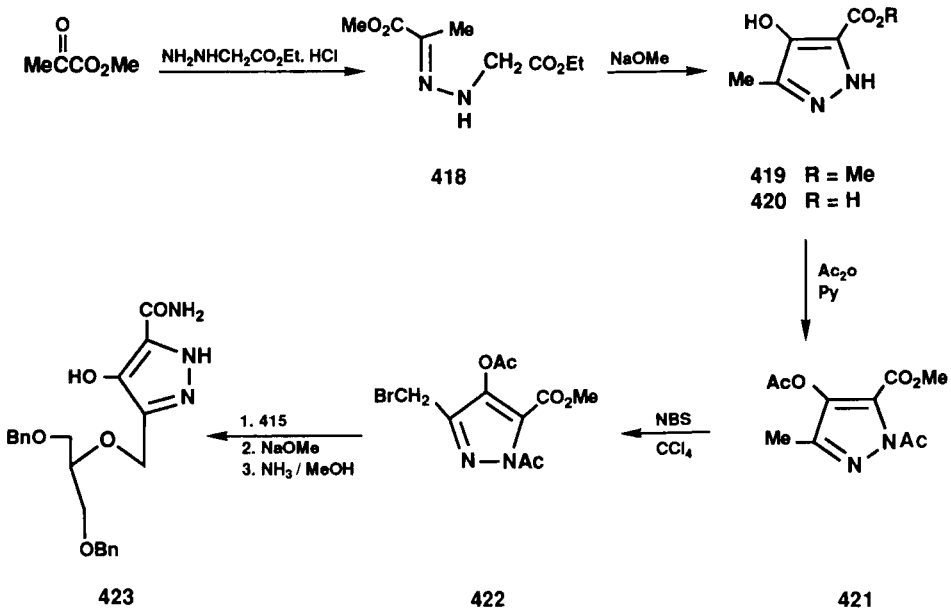


SCHEME 81

The acyclic analog of pyrazofurin that possesses the side chain of ganciclovir was prepared by constructing the heterocyclic ring, prepared from the hydrazone of methyl pyruvate **418,** by heating with the sodium alkoxide in THF to give **419** and **420,** followed by esterification and acetylation to **421.** Its bromination gave **422,** which, upon reaction with **415** and then deprotection, gave **423,** which has no antiviral activity (91MI4).

7. *Carboacyclic Analogs*

The carbo analog (Penciclovir) **431** of DHPG was prepared starting from diethyl malonate (**424**). Upon alkylation **424** gave **425,** which was reduced and benzylated to **426.** The latter was converted to **427** in four steps and then reacted with the sodium salt of guanosine, followed by debenzylation by a phase transfer catalysis to give **431** (84MI4). A shorter route to the carbo analog of DHPG **431** was carried out starting with triester **429.** Its reduction gave the triol, which upon partial protection gave **428,** followed by the conversion of the unprotected hydroxy group to a bromine to give **430** (85TL4265). Alkylation of 2-amino-6-chloropurine with the bromodeoxy derivative **430** gave the 9-isomer, whereas the 7-isomer was barely detect-



SCHEME 82

able. Acid hydrolysis of the 9-isomer converted the 6-chloro to the 6-oxo function and removed the acetonide group to give **431** (87JMC1636), which showed the highest activity against herpes simplex virus type 1 and to a lesser extent type 2. In some tests it is more active than acyclovir (87JMC1636; 92MI1). The dihexanoate ester is the most active ester (84MI4; 87JMC1636). The same strategy was used to prepare C-substituted analogs starting with substituted ethyl bromoacetates [88JCS(P1)2757].

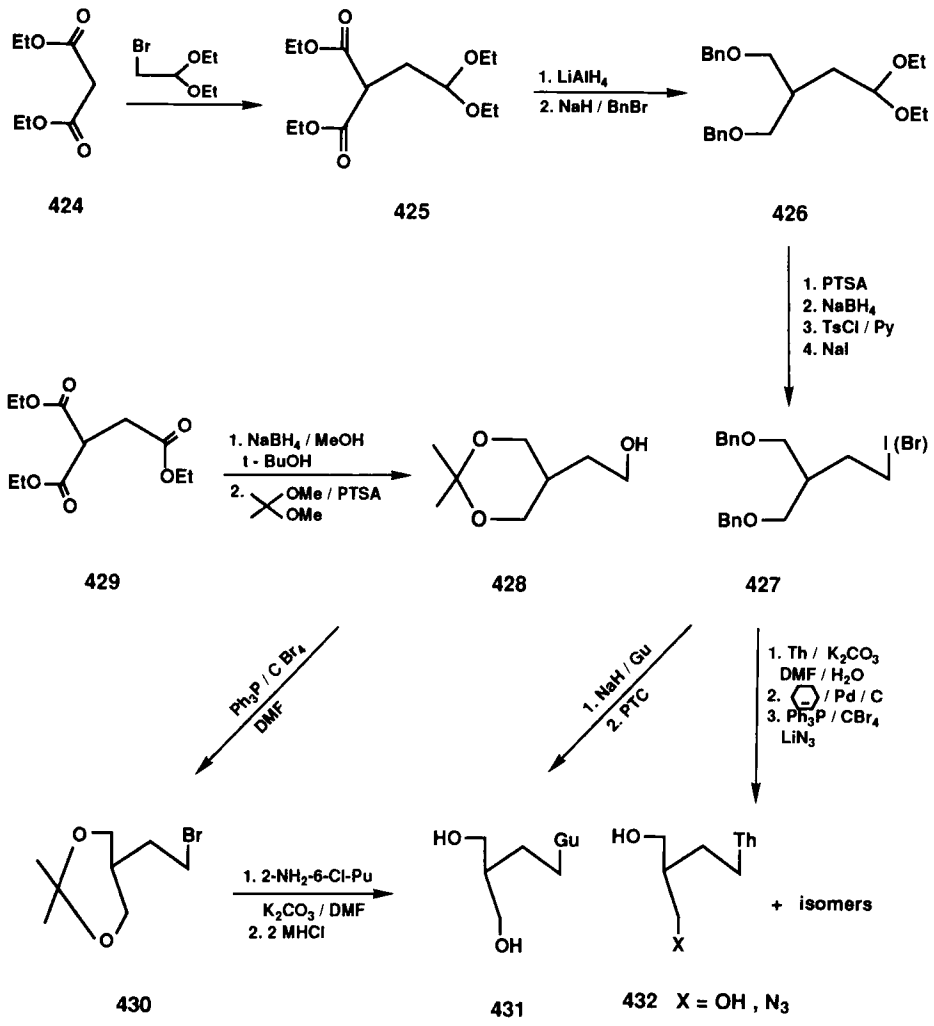
Tosylation of the isobutylidene analog of **428** followed by reaction with iodine and coupling with the sodium salt of guanine and then deprotection gave **431** (86JMC1384).

Alkylation of the thymine with bromide **427** presents a problem. The best condition to introduce the alkyl group onto N-1 is to use excess thymine and K_2CO_3 in DMF–H_2O, whereby the product was obtained in addition to the N-3 mono- and N-1, N-3 dialkylated derivatives, as well as monobenzylated derivatives. Debenzylation gave **432** (X = OH), whose reaction with $Ph_3P/CBr_4/LiN_3$ gave **432** (X = N_3) in low yield as a racemate (92MI5).

The crystal and molecular structures of 9-[4-hydroxy-3-(hydroxymethyl)-butyl]guanine (BRL39123; Penciclovir) and its prodrug 9-[4-acetoxy-3-(acetoxymethyl)butyl]-2-aminopurine (BRL42810, Famciclovir) were reported (90MI2).

The 2,6-dichloropurine analog **434** was prepared in two ways, either by alkylation of the base with 2-acetoxymethyl-4-iodobutylacetate to give **434** and its 7-isomer, or by chlorination of **433.** Hydrolysis of **434** gave **435,** in which the chlorine could be substituted with amines to give **436** [89JCS(P1)2207]. The 2-amino-6-iodopurine may also be used as a base in the coupling (90EUP352953). The respective 2-*N*-hydroxyguanine showed potent antiherpes virus activity in a cell culture test [89JCS(P1)2207]. Functional group conversion of one hydroxyl group of **436** was achieved via the bis(monomethoxytrityl) derivative **437** by bromination and deprotection to **438** (X = Br). Its conversion to the azide followed by reduction gave the amine whose formylation gave the formyl derivative, which showed moderate antiherpes virus activity, whereas **438** (X = N_3) showed only weak activity [88JCS(P1)2777].

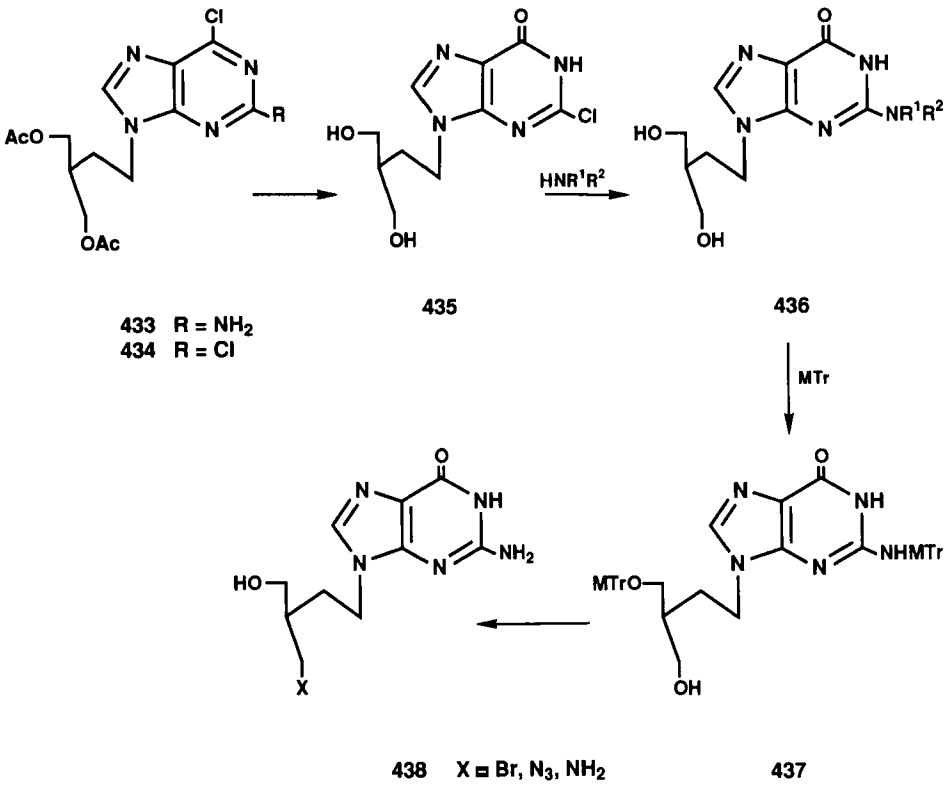
The corresponding ethers proceeded from diol **439.** Selective acetylation of **439** and then methylation gave **441** (R = H). In contrast, selective allylation of **439** followed by hydroxylation gave **440.** Periodate oxidation and reduction gave the corresponding alcohol, whose acetylation gave **441.** Debenzylation by catalytic hydrogen transfer or hydrazinolysis followed by bromination gave **442;** subsequent alkylation of the base and then deprotection gave **443** [88JCS(P1)2777]. A weak antiherpes virus activity was observed for **443** (R^1 = CH_2OH).



SCHEME 83

8. *Modified Carboacyclic Analogs*

Carboacyclic nucleoside analogs modeled on the unsaturated carbocyclic nucleoside analog neplanocin have been synthesized. The key intermediate for this synthesis was **445,** which was prepared from the 1,3-bisbenzoxyacetone **408** by reaction with triethyl phosphonoacetate to give **444,** followed

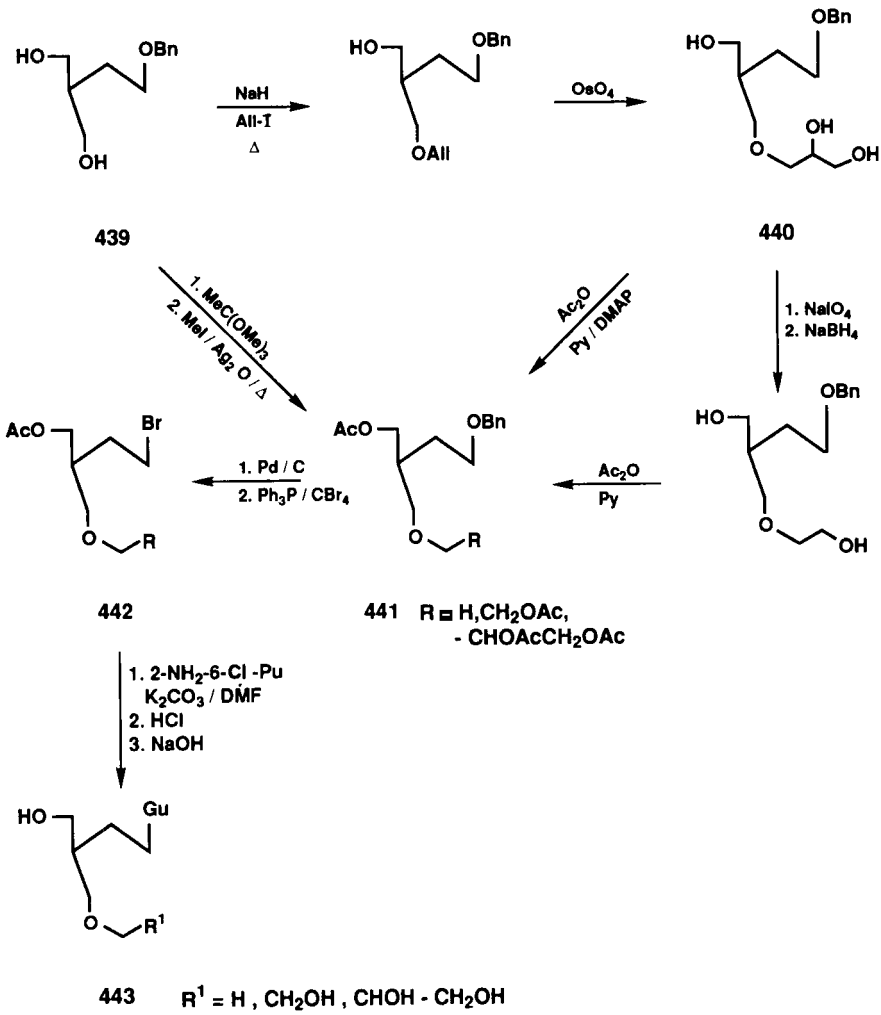


SCHEME 84

by reduction of the ester group to give the alcohol that upon attempted tosylation gave the chloro derivative **445.** Coupling of either adenine or the guanine precursor 2-amino-6-chloropurine with **445** formed the nucleosides **446,** whose debenzylation gave **447.** In the case of a guanine precursor, further treatment with alkali was required to obtain the guanine analog, which exhibited significant antiviral activity against HSV-2 (87JMC943).

The preparation of 2,2-bis(hydroxymethyl)cyclopropyl analogs **450** and **452** was accomplished starting with the cyclopropane derivatives **448,** which, when reduced, benzoylated, ozonized, reduced, and then tosylated, gave **449.** Coupling of the latter with adenine and then debenzoylation gave **450,** whereas coupling with 2-amino-6-chloropurine gave **451** followed by acid hydrolysis to give the guanosine **452** (88JMC2304).

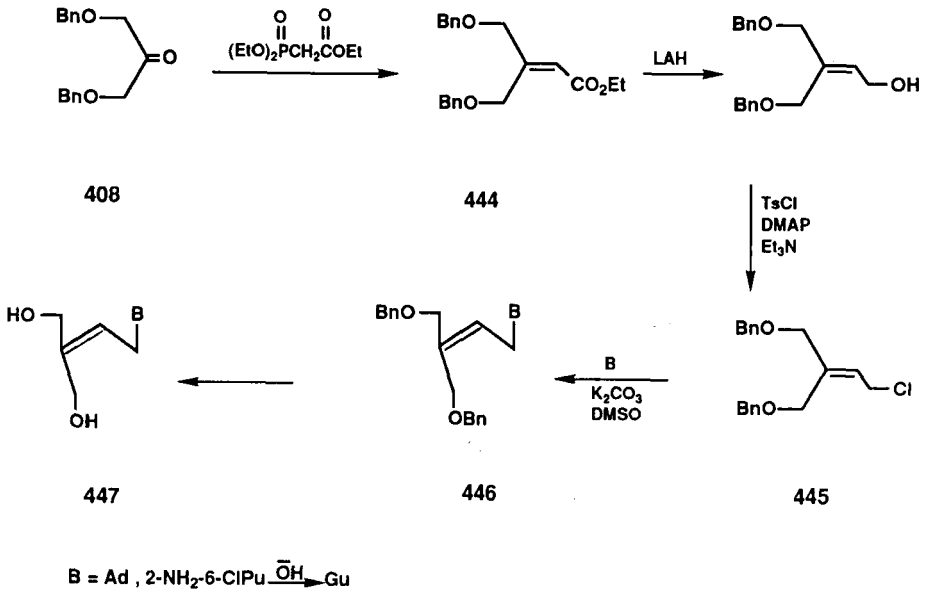
The branched-chain analogs were prepared as shown previously for the nonbranched ones from triester **429.** Alkylation of its anion with iodometh-



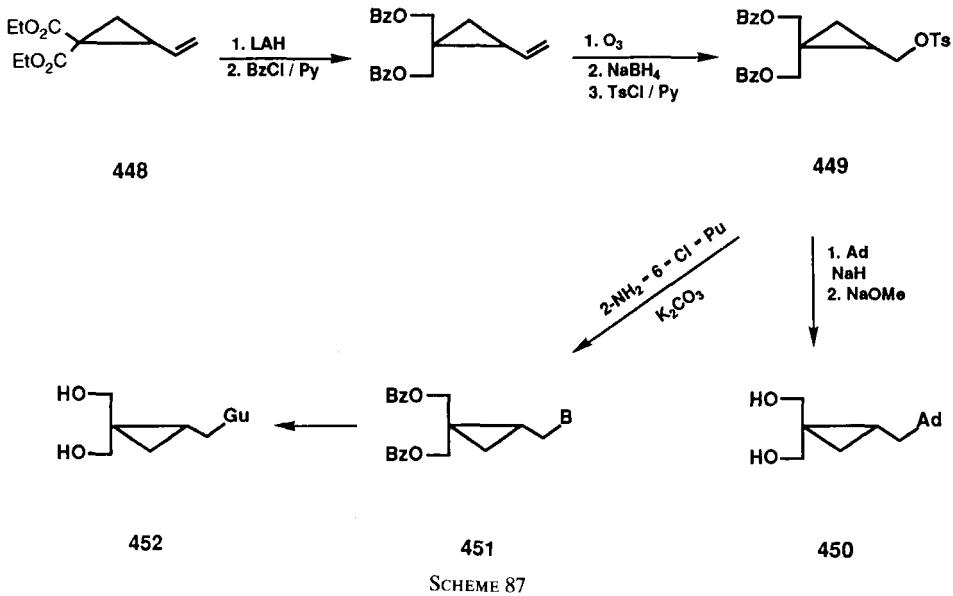
SCHEME 85

ane or benzyl chloromethyl ether gave **453,** followed by reduction with sodium borohydride or $LiAlH_4$ to give the respective triol. Acetonation of the triol was accomplished with little selectivity, whereby **454a** was formed in appreciable quantities in addition to **454b.** Bromination of the latter gave **455.** Coupling of **455** with 2-amino-6-chloropurine gave **456,** whose hydrolysis gave the guanosine analog **457** [88JCS(P1)2767].

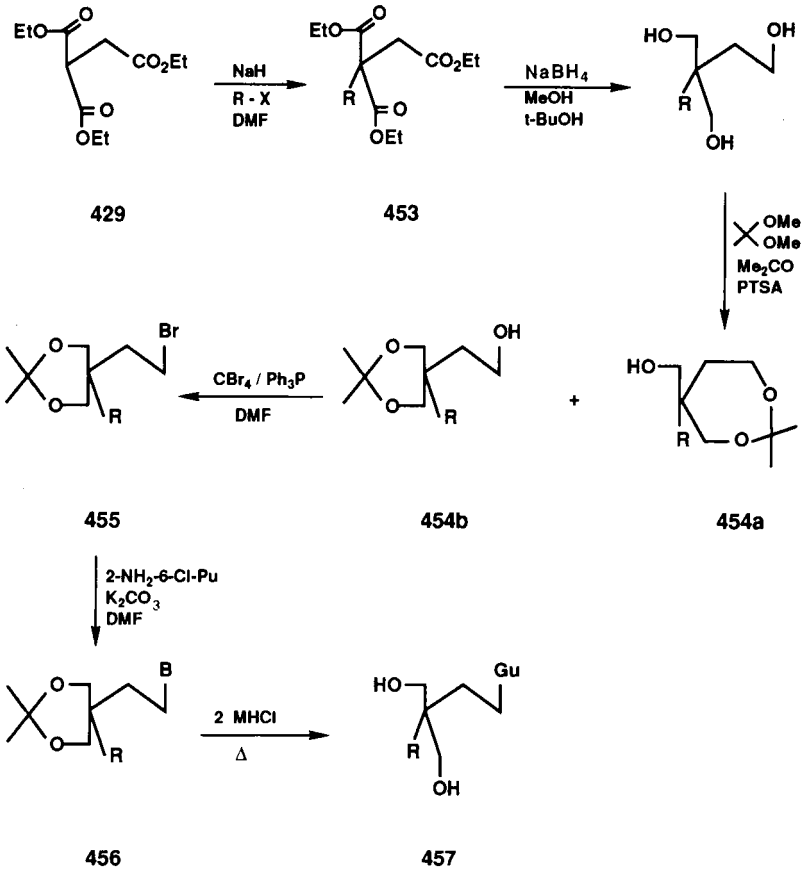
The fluoro analog **463** was prepared from diethyl acetoxymalonate **458** by alkylation of its anion with benzyl-2-bromoalkyl ether to give **459,** whose



SCHEME 86



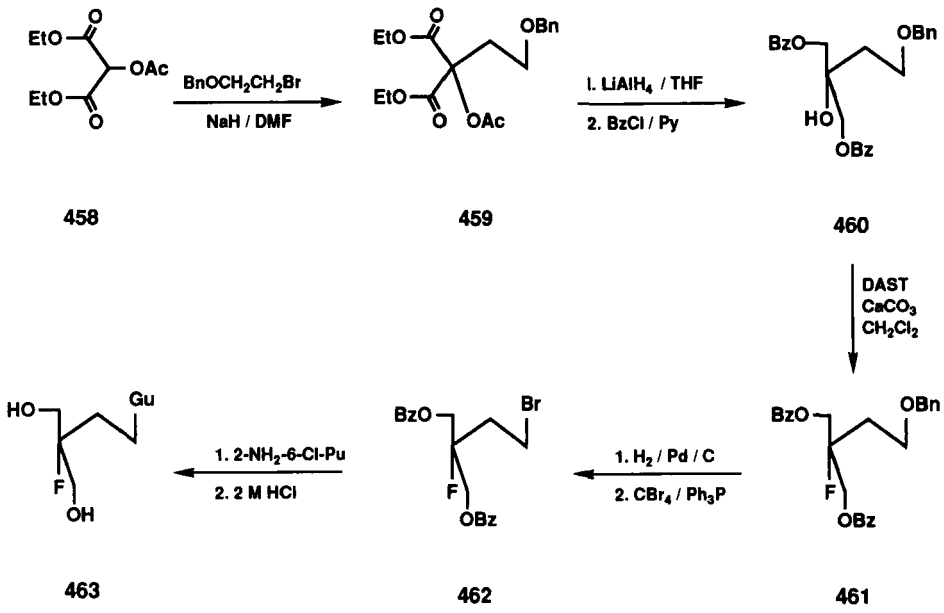
SCHEME 87



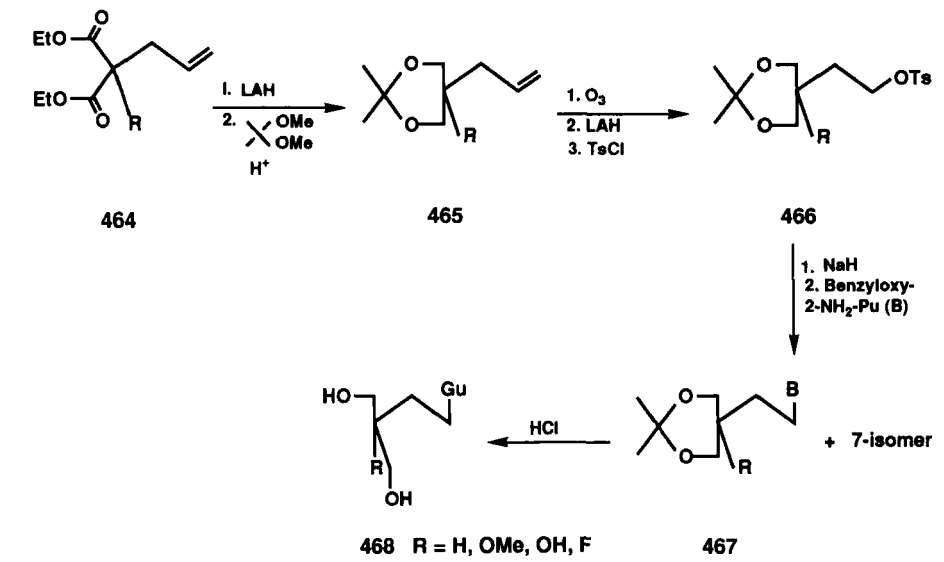
SCHEME 88

reduction followed by benzoylation gave **460.** Fluorination of **460** gave **461.** Debenzylation followed by bromination gave **462,** which was used in the alkylation of 2-amino-6-chloropurine followed by acidic hydrolysis to give **463** [88JCS(P1)2767].

An alternative route to the carba-ganciclovir and its modified side chain was started by the malonate derivatives **464,** where the allyl group serves as a masked 2-hydroxyethyl function. Thus, reduction of **464** gave the respective diol that was protected as the isopropylidene **465,** which upon ozonolysis, reduction, and tosylation gave **466.** The respective tosylates were used in the alkylation of 2-amino-6-benzyloxypurine to give **467,** in addition to the 7-isomeric product. Hydrolysis gave the carba-ganciclovir analog **468** (89JHC1261). Their antiviral activities were evaluated.



SCHEME 89

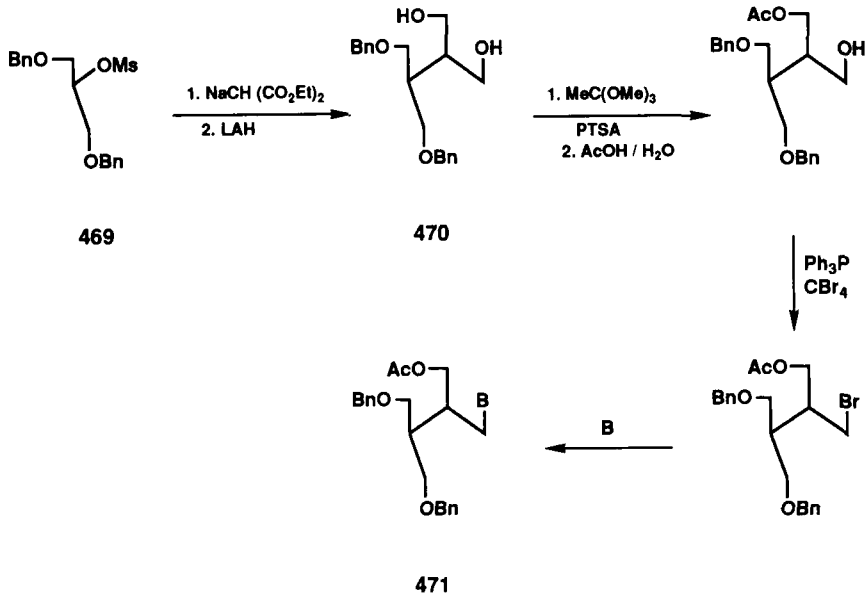


SCHEME 90

The alcohol **470** was prepared from the mesylate **469** by reaction with diethyl malonate followed by reduction to give **470,** whose selective acetylation was carried out by reaction with trimethyl orthoacetate followed by acid hydrolysis of the cyclic orthoester intermediate. Bromination and then coupling gave **471** [88JCS(P1)2757].

The analogs **479** and **480** were prepared from the *O*-protected glycoaldehyde diethylacetals **472** by a *trans*-acetalization to **473,** which was chlorinated to **474** and then reacted with diethyl malonate followed by reduction to give **475** or **476.** Cyclohexylidenation and then debenzoylation of **475** gave **481.** Benzoylation of **476** gave **477,** which upon debenzylation, tritylation, and then fluorination gave **478.** Detritylation of the last gave the respective alcohols. The alcohols from **478** and **481** were converted to the bromides and/or the mesylates. Alkylation of 2-amino-6-chloropurine with these bromides or mesylates gave **479** and **480,** which were converted to the racemic 9-substituted guanines [88JCS(P1)2757].

Synthesis of the 1′-methoxy derivative **484** commenced with the alkylation of the anion of diethyl malonate with a suitable bromoacetal, followed by reduction to give **482,** which upon acetylation and then reaction with acetyl chloride and thionyl chloride gave the α-chloroether **483.** Reaction of **483** with the trimethylsilylated 2-*N*-acetylguanine using tin (IV) chloride

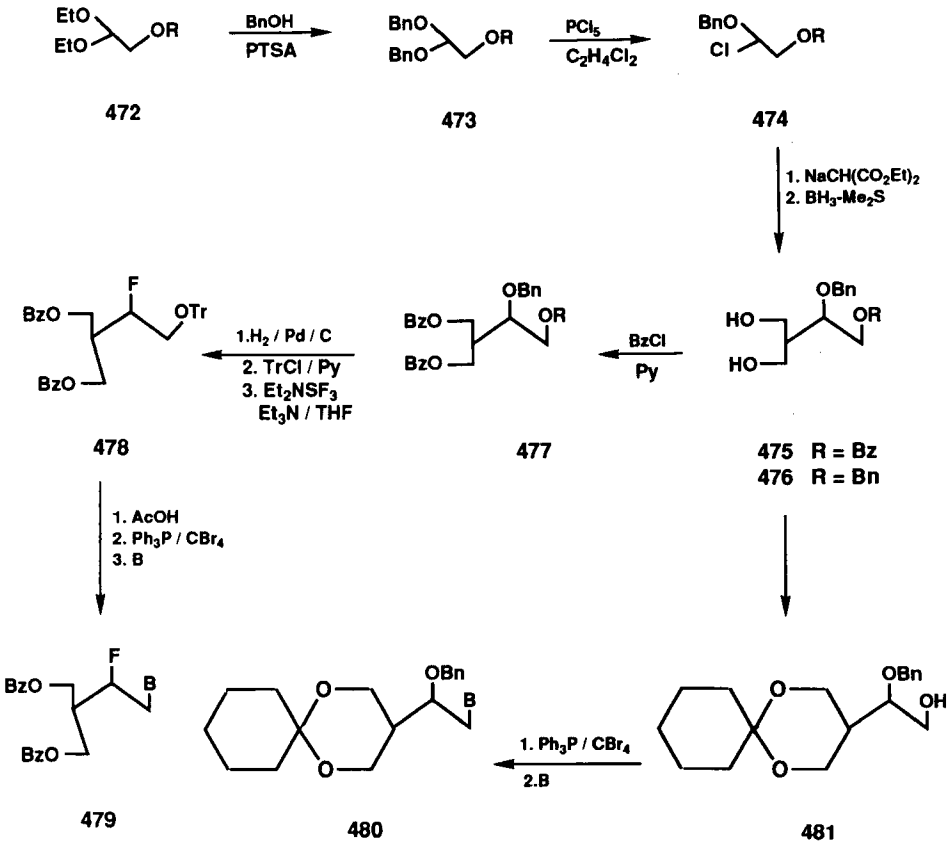


469 **470** **471**

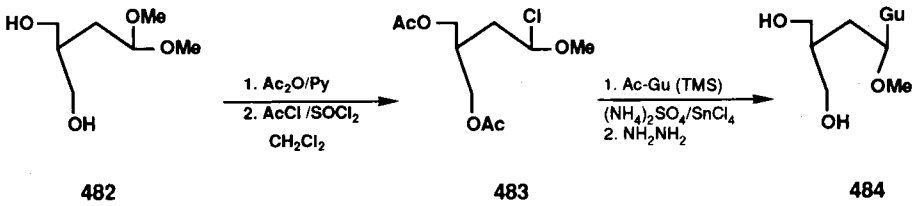
SCHEME 91

as a catalyst gave a mixture of 9- and 7-alkylation products, whose deacetylation gave **484** and its isomeric product, respectively [88JCS(P1)2767]. All of these acyclonucleosides with branched chains were tested for antiviral activity in cell cultures. The most active was the 3′-fluoro, but it had only about one-third of the activity of the lead compound 9-(4-hydroxy-3-hydroxymethylbutyl)guanine against herpes viruses.

This type of acyclic nucleoside could be prepared by a Michael addition process. Thus, when 2-amino-6-chloropurine was reacted with **485,** and 8 : 1 mixture of the N-9 (**486**) and N-7 cyclopropylpurines was produced. When the chloroethylidene malonate was used, the ratio became 40 : 1. Catalytic hydrogenation of **486** in presence of base effected both dehalogenation and 1,2-cyclopropane bond fission to provide **487.** Its reduction and acetylation gave Famciclovir **488** (91EUP420559; 92TL4609).



SCHEME 92

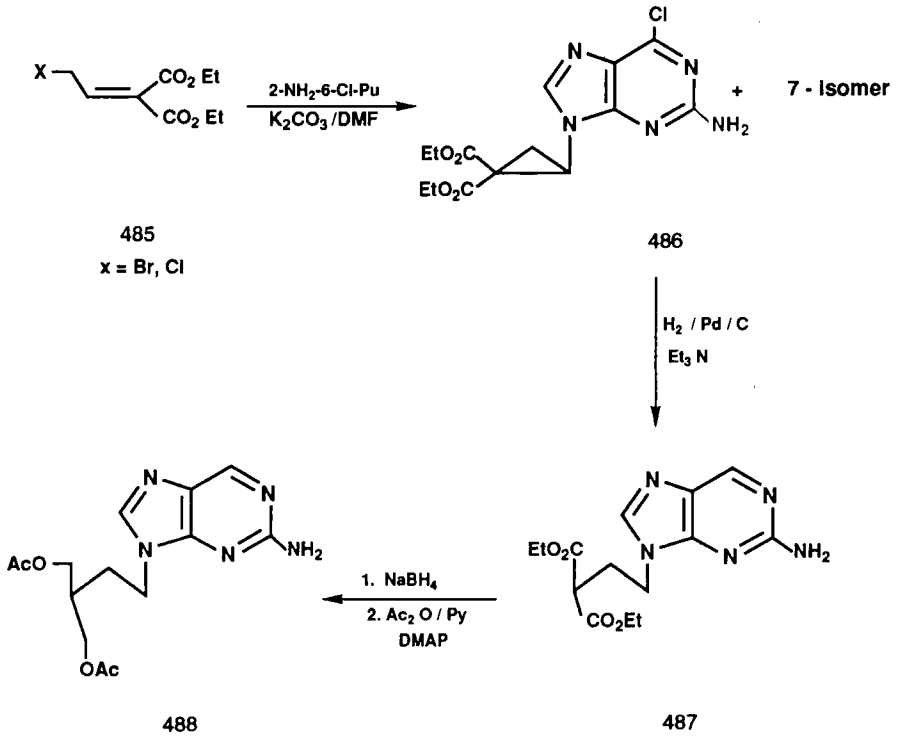


482 **483** **484**

SCHEME 93

9. *Carboacyclic Analogs via Heterocyclic Ring Construction*

The synthesis of the carboacyclic analogs may be performed by constructing the heterocyclic ring on a suitable functionalized side chain. Thus, the acetal **489** was synthesized in a similar manner to **426.** Its reaction with hydroxylamine hydrochloride gave a mixture of the oxime **490** and nitrile



485
x = Br, Cl

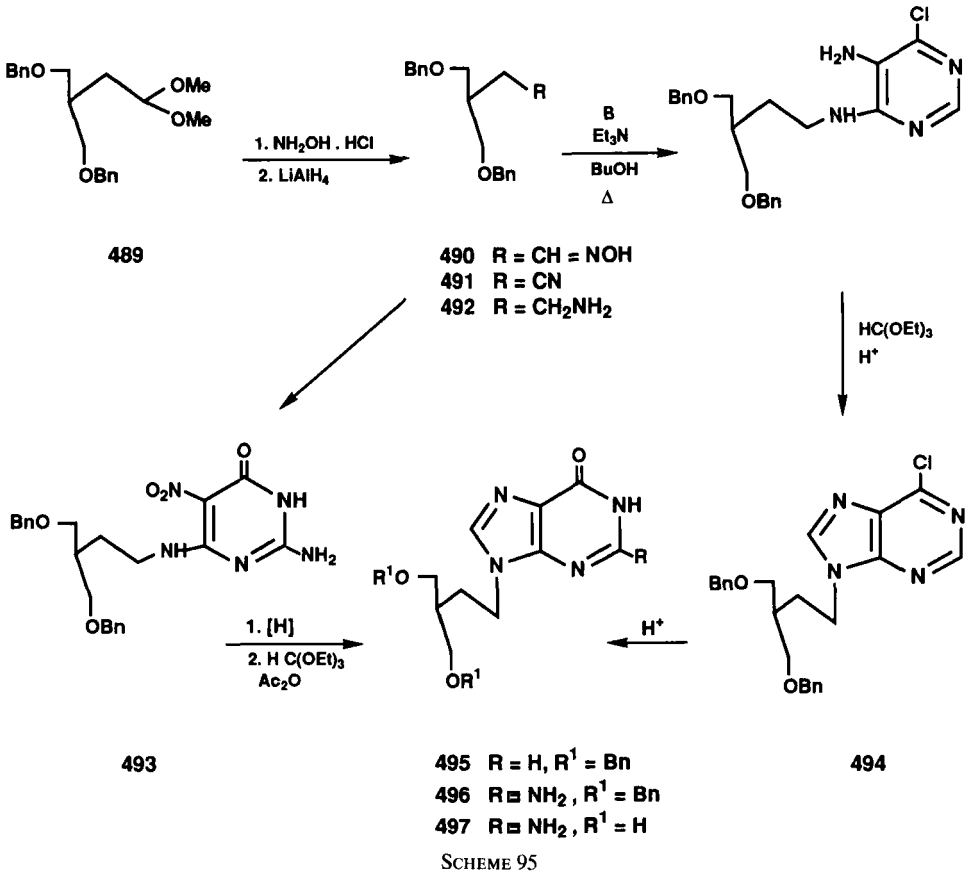
486

488 **487**

SCHEME 94

491, which upon reduction gave **492.** Reaction of **492** with 5-amino-4,6-dichloropyrimidine followed by cyclization with ethyl orthoformate gave **494,** which upon hydrolysis gave the hypoxanthine analogs **495;** its amination, however, gave the adenine analogs (72SC345). The respective guanine analog **496** was prepared by cyclization of **493.** Debenzylation of **496** gave **497.** The crystal and molecular structure of Penciclovir (BRL 39123) and Famciclovir (BRL 42810) were determined. In the former, the plane of the acyclic N-9 substituent is orthogonal to the purine ring. It has an extensive network of intermolecular hydrogen bonds. In Famciclovir, however, there are no major hydrogen bonding interactions, but there are π–π interactions between parallel overlapping pyrimidine moieties (90MI2).

The pyrimidine ring in **499** could be constructed by the condensation of **492** with acrylamide **498,** followed by base-catalyzed cyclization to **499**



489

490 R = CH = NOH
491 R = CN
492 R = CH_2NH_2

493

495 R = H, R^1 = Bn
496 R = NH_2, R^1 = Bn
497 R = NH_2, R^1 = H

494

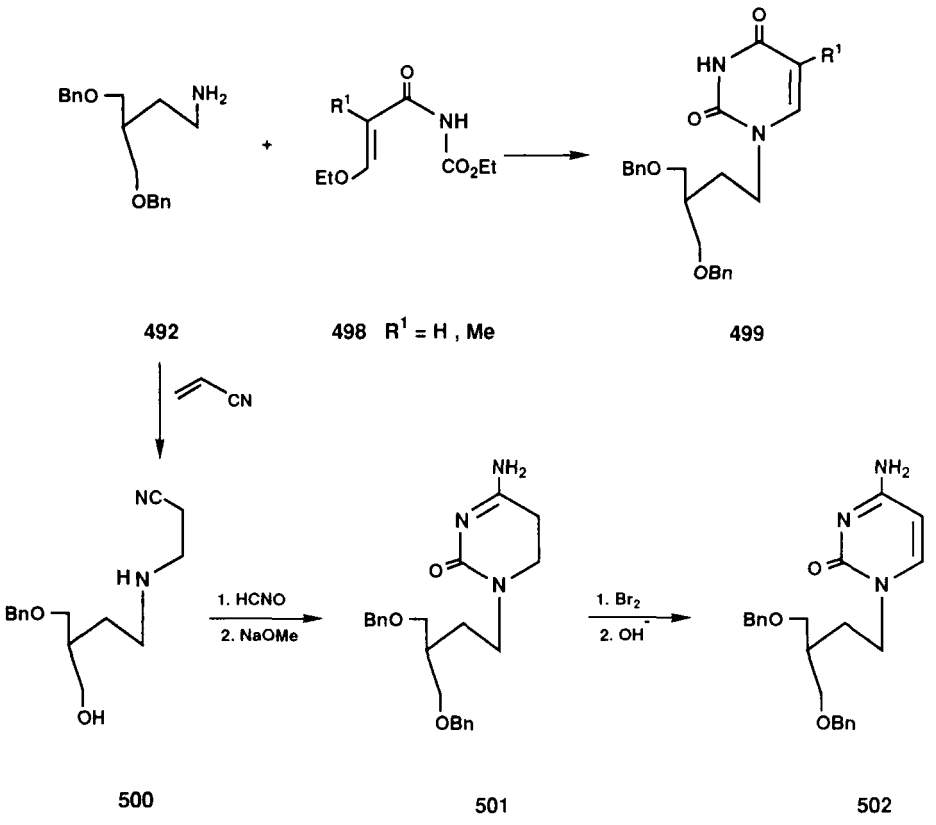
SCHEME 95

(72SC345). Cyanoethylation of **492** gave **500,** whose cyclization gave **501,** which upon bromination and dehydrobromination gave **502** (72SC345).

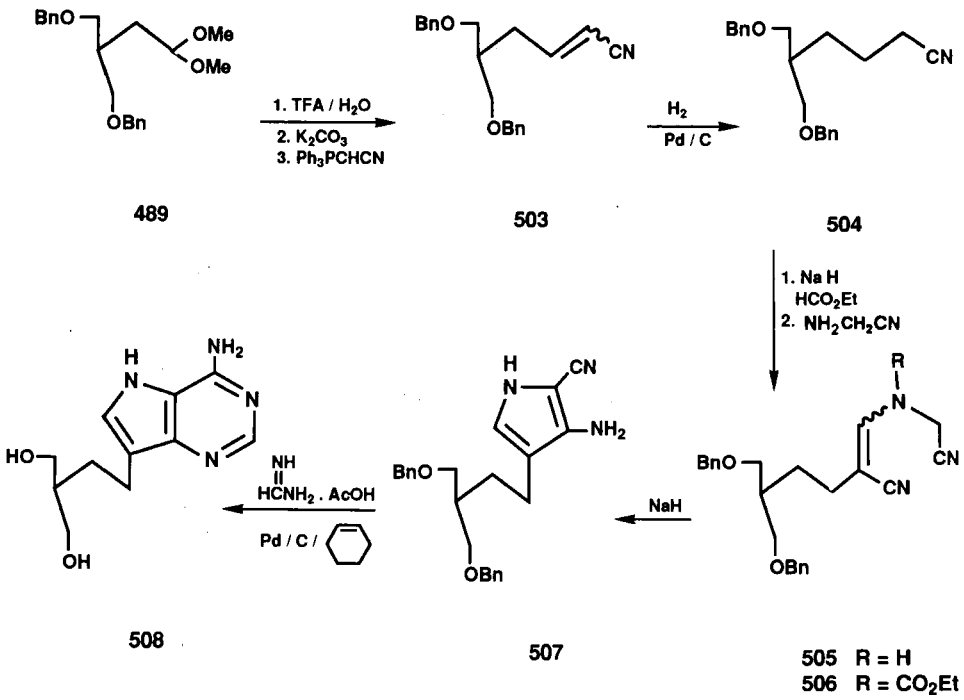
10. *Carboacyclic C-Nucleoside Analogs*

The carboacyclic *C*-nucleosides could be constructed from **489** by cyanomethylation to give **503,** which upon reduction gave **504.** Iminoolefination of **504** gave **505,** whose reaction with ethyl chloroformate gave **506,** which was cyclized to the pyrrole **507;** the pyrimidine ring then was formed to give **508** [91JCS(P1)195].

A series of conformationally restricted acyclic pyrimidine nucleosides fixing the base–sugar orientation in the anticonformation by forming a carbon bridge between them has been prepared. This was based on the

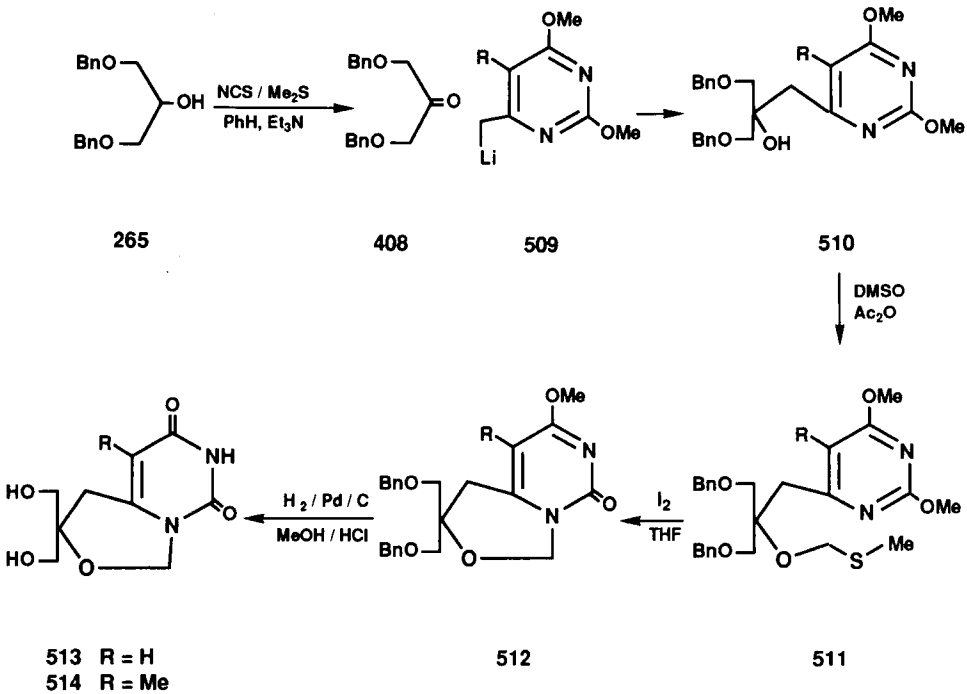


SCHEME 96



SCHEME 97

hypothesis that if the nucleoside is to be a good substrate for HSV-TK and be active against herpes viruses, it must exist in the anti conformation rather than the syn conformation. Thus, the C-6 side chain was connected via an addition reaction of the lithiated 6-methyl pyrimidine derivatives **509** with 1,3-bis(benzyloxy)-2-propanone **408** to give **510.** The lithio derivatives were prepared from the pyrimidine bases with LDA in tetrahydrofuran. The tertiary hydroxyl group of the side-chain group was smoothly converted to **511** on treatment with a mixture of acetic anhydride and anhydrous dimethyl sulfoxide. Ring closure of **511** to bicyclic **512** was accomplished with iodine in dry tetrahydrofuran. An initial electrophilic activation of the sulfur atom of the (methylthio)methyl group by the iodine took place to generate a reactive sulfonium species, which promoted the nucleophilic attack at the methylene position by the nitrogen of the pyrimidine ring. Deprotection of **512** gave **513** or **514,** whereas the cytidine derivative was obtained by debenzylation with boron trichloride, followed by a displacement of the methoxy group using saturated methanolic ammonia (92JOC3354).



SCHEME 98

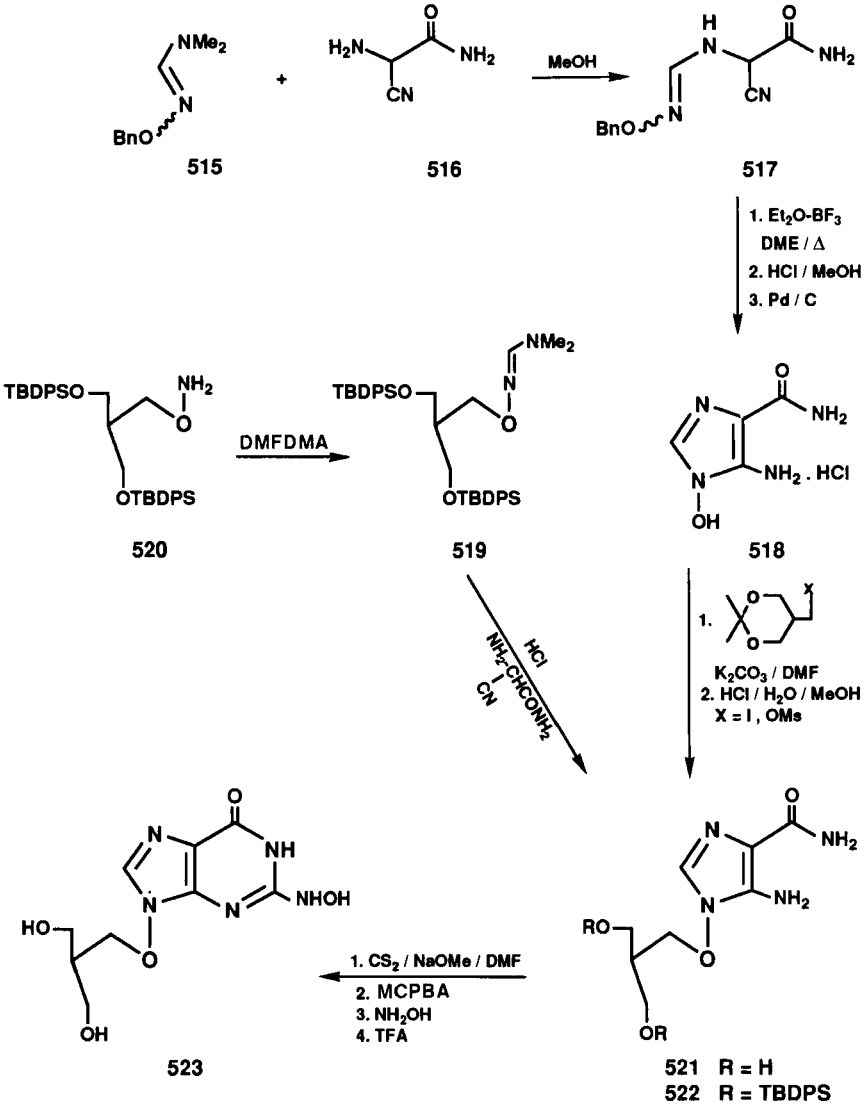
11. *Translocation of Oxygen with Carbon and Aza Analogs*

Analogs with a translocated atom of the ether linkage by a carbon atom have been also prepared. Thus, reaction of 2-amino-2-cyanoacetamide hydrochloride **516** with *N,N*-dimethyl-*N'*-benzyloxymethanimidamide **515** in methanol gave **517** as an unstable intermediate. Cyclization of **517** with the Lewis acid diethylether–boron trifluoride in 1,2-dimethoxyethane followed by catalytic hydrogenolysis over 10% palladium on charcoal afforded **518,** isolated as its hydrochloride. Its alkylation with the 5-iodomethyl-2,2-dimethyl-1,3-dioxane, in the presence of potassium carbonate, gave the 1-alkoxyimidazole. A similar yield was obtained by using the mesylate and catalytic amounts of lithium iodide. Deprotection under acidic conditions gave the imidazol-1-yloxyalcohols **521** (90S893).

Alternatively, the construction of these nucleosides was achieved from the alkoxyamine derivative **520** by conversion to the respective formamidine **519.** Transamidination followed by boron-trifluoride-catalyzed cyclization gave the imidazoles **522.** Their cyclization was effected using sodium methyl-

xanthate to give the purine thiolates, which upon oxidation with MCPBA gave the sulfonate, which directly reacted with hydroxylamine. Deprotection gave **523** [89JCS(P1)2207].

The alkoxyamine **524** was converted to the urea derivative **525,** whose cyclization with 3,3-dimethyloxypropionate or ethyl-3,3-diethoxy-2-methyl-

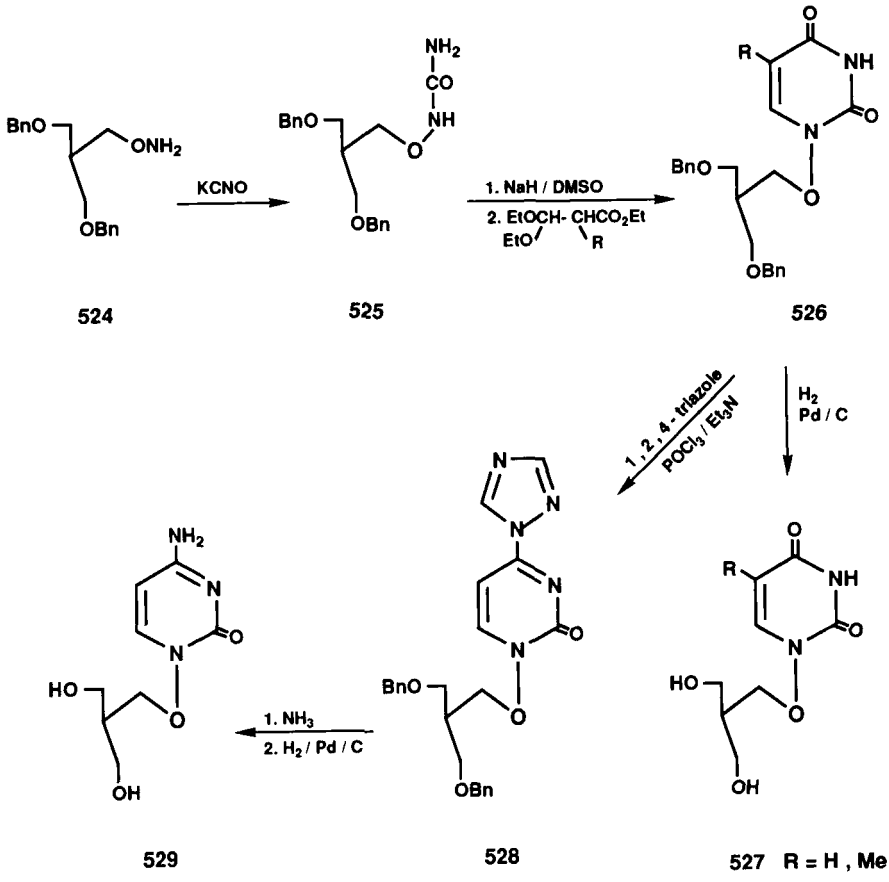


SCHEME 99

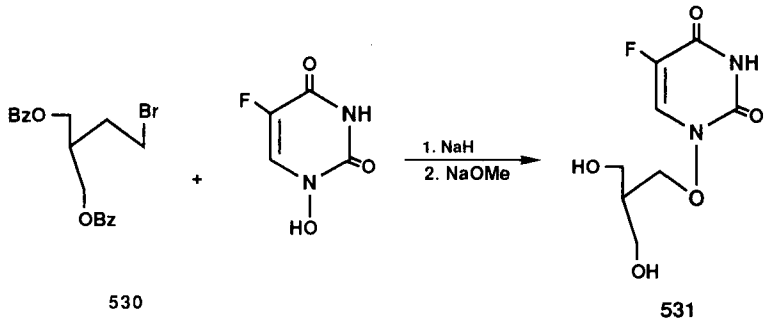
propionate was effected to give the pyrimidine derivatives **526.** Their catalytic hydrogenation gave **527** (88TL4013). The cytosine derivative **529** was prepared via the triazolo derivatives **528,** which upon aminolysis and deprotection gave **529.** None of these compounds had significant antiviral activity.

The 5-fluoro analog **531** was prepared by alkylation of 5-fluoro-1-hydroxyuracil, via initial formation of its dianion with the appropriately functionalized halide **530** and then conventional deprotection [90JCS(P1)2175]. No significant activity was noted against herpes simplex virus type 1 and 2, varicella zoster, cytomegalovirus, or Epstein–Barr virus.

Replacement of the oxygen by nitrogen in the preceding analogues led to the 9-alkylaminoguanines **536.** They were prepared from the 9-aminogua-



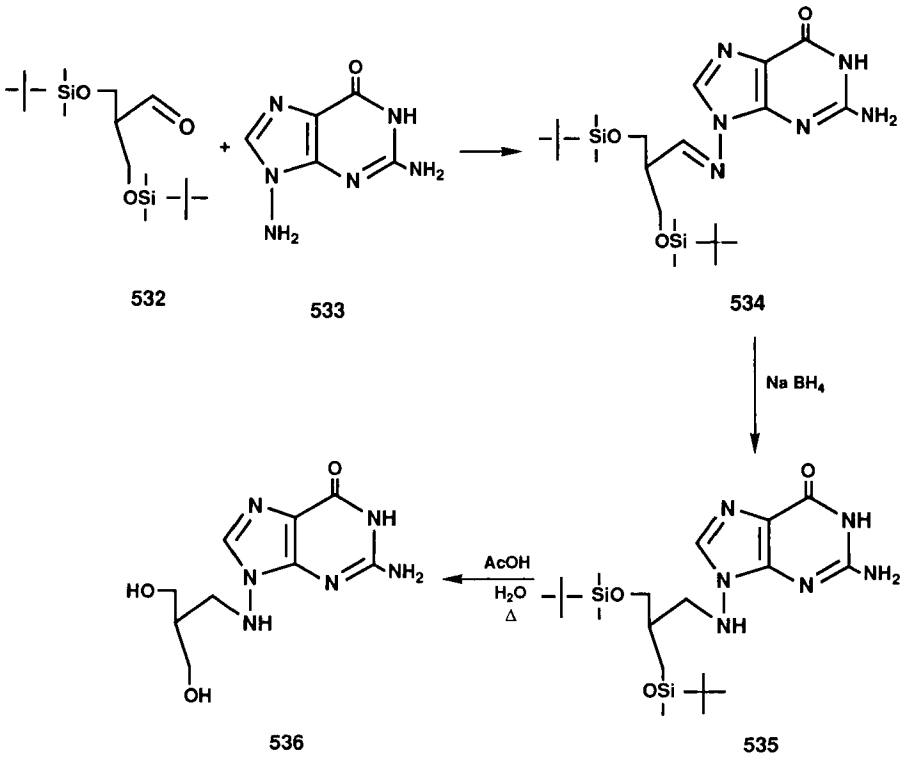
SCHEME 100



530 531

SCHEME 101

nine **533,** by condensing it with aldehyde **532** to give **534.** Reduction of **534** gave **535,** which was followed by desilylation to give **536** (88TL5995). They are selective antiherpes virus agents, although less potent than analogous 9-alkyl and 9-alkoxyguanines.



532 533 534 535 536

SCHEME 102

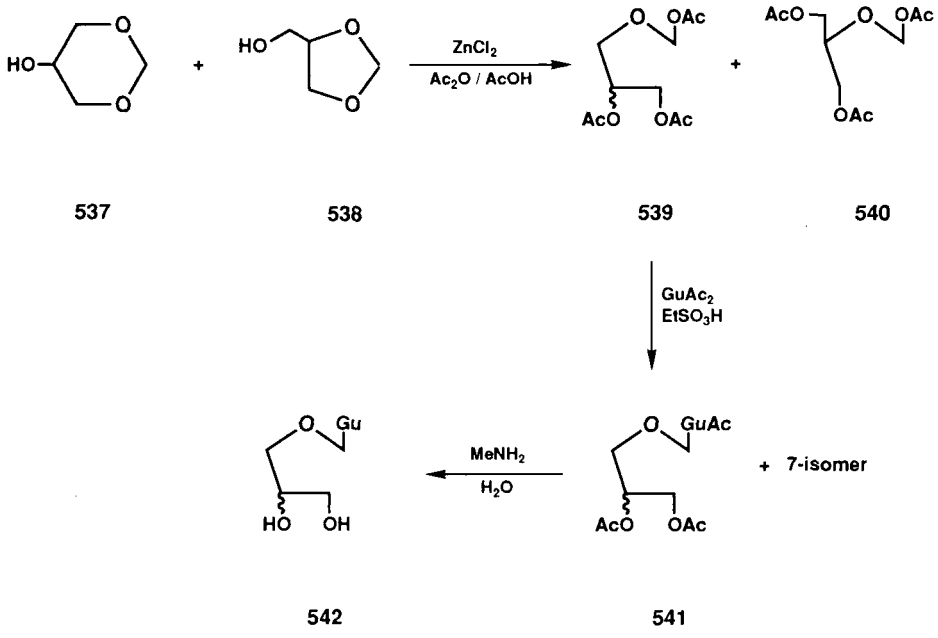
B. 1′,2′- AND 4′,5′-*diseco*-NUCLEOSIDES (TYPE 2.2)

1. *General Methods of Construction*

Acetoxymethyl ethers **539** and **540** could be prepared from the mixture of glycerol formals **537** and **538.** Reaction of **539** with $GuAc_2$ gave N-9 (**541**) (and N-7) guanine derivatives as racemic forms whose deacetylation gave **542** (84TL905; 85JMC926).

Alkylations of benzimidazole **547** and benzotriazole **548** with the triacylated derivatives **543** or **545** and their dideoxy derivative **544** gave after deprotection **550** and **551,** respectively (88KFZ714). The benzotriazoles had greater antiviral activity to enterovirus than the benzimidazoles. The acyclic derivatives derived from **549** are only moderately virucidal to some RNA-containing viruses (89KGS493). The reaction of **546** with 1(3)-*H*-imidazo[4,5-*b*]pyridine gave the 1- and 3-isomers **553** and **554** (90MI1). **552** was formed similarly.

The respective optical isomers (*R*)- and (*S*)-iNDG were prepared by reacting the enantiomers of the 1,2-di-*O*-benzylglycerols **556** and **565** with paraformaldehyde and anhydrous HCl to give the corresponding chloro-



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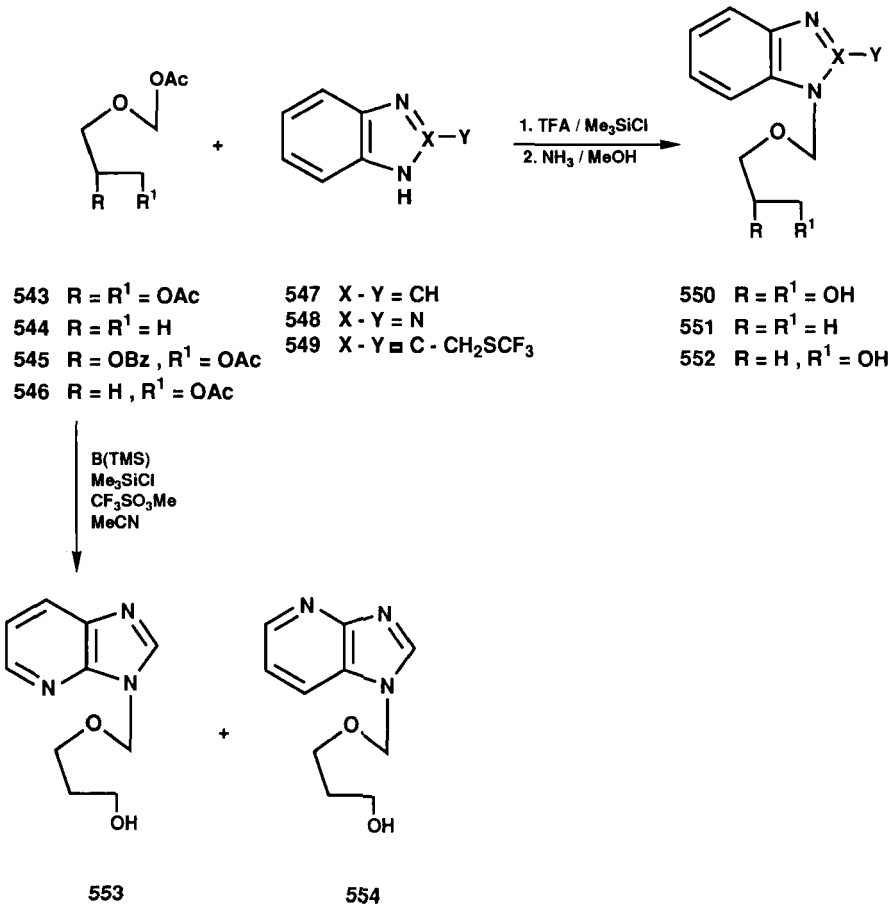
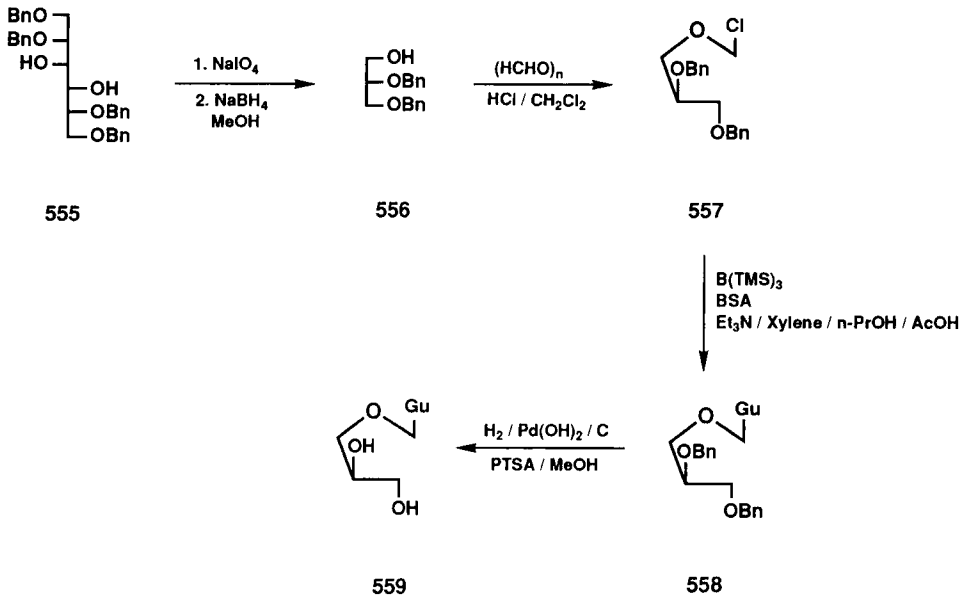


SCHEME 104

methyl ether **557** and its isomer **566,** respectively. They reacted with the tris (trimethylsilyl)guanine to give **558** and **567,** respectively. Their catalytic hydrogenation gave the corresponding **559** and **568** (85JMC926). The precursor for the chiral glycerol **556** was the D-mannitol derivative **555,** whose periodate oxidation and reduction gave **556,** whereas the other isomer **565** was prepared from the D-mannitol derivatives **560,** whose oxidation and reduction gave **561.** The last, upon benzylation and hydrolysis, gave **562,** which upon tritylation gave **563;** subsequent benzylation gave **564.** Hydrolysis then gave **565.** The racemic form exhibited potent antiviral activity (84TL905). The (*S*)-iNDG was found to be more active than the *R* enantiomer against HSV-1 and HSV-2 in cell culture; it had an ED_{50} comparable



SCHEME 105

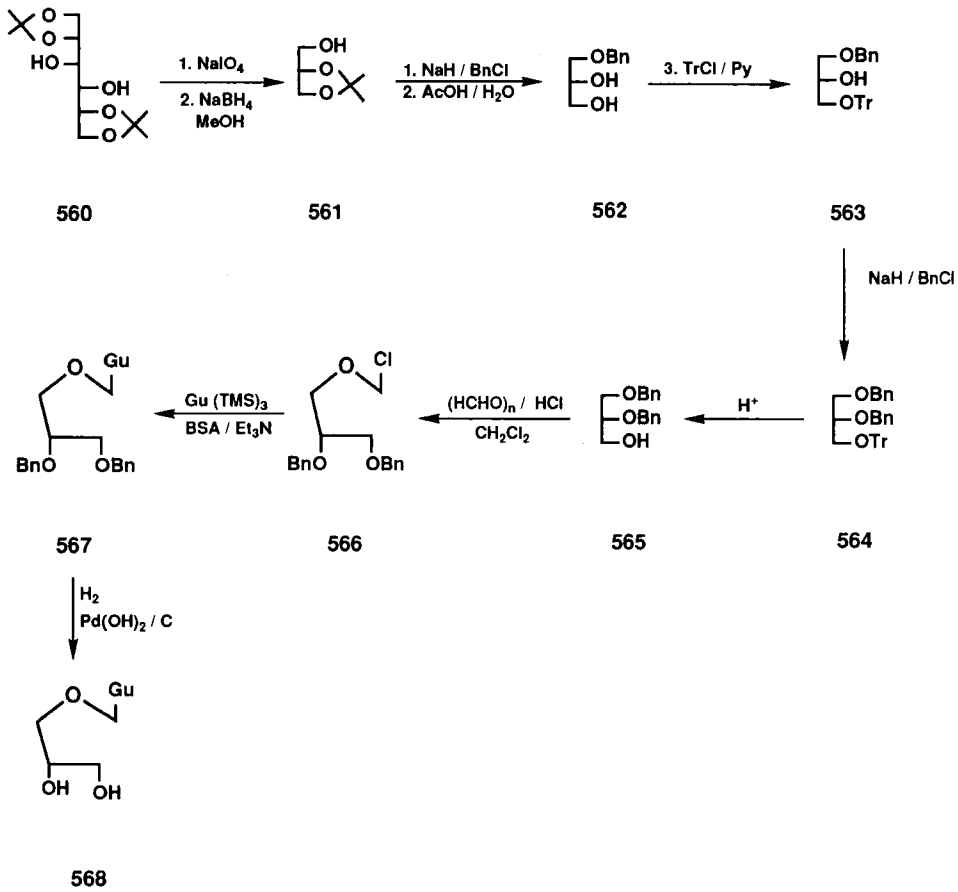
to those for ACV and 2′ NDG. The inferior activity of (*R*)-iNDG parallelled the poor inhibition of viral DNA polymerase by its phosphorylation products. In mice (*S*)-iNDG was less efficacious than 2′NDG, but comparable to or more active than ACV (85EUP130126; 85JMC926).

An alternative source for the chiral nucleoside **559** utilizes methyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**569**); this was chloromethylated to give **570,** which upon reaction with 2-amino-6-benzyloxypurine gave **571.** Debenzylation of **571** gave **572,** whose periodate oxidation followed by reduction gave the glycerol derivative **573,** which upon acid hydrolysis gave **559** (85TL1815).

2. *Deoxyazido and Deoxyamino Analogs*

1-Hydroxy-2-azido-3-propoxymethylpyrimidines **577** were synthesized from **574** by displacement with azide ion to give **575,** followed by ring-opening with acetyl bromide to give **576,** which upon reaction with base and deacetylation gave **577** (89MI7).

The DL-serine uracil derivative **580** was prepared from DL-serine methyl ester hydrochloride by *N*-benzoylation to give **578;** chloromethylation gave **579,** which then was substituted by the silylated uracil (88ZOB2404).

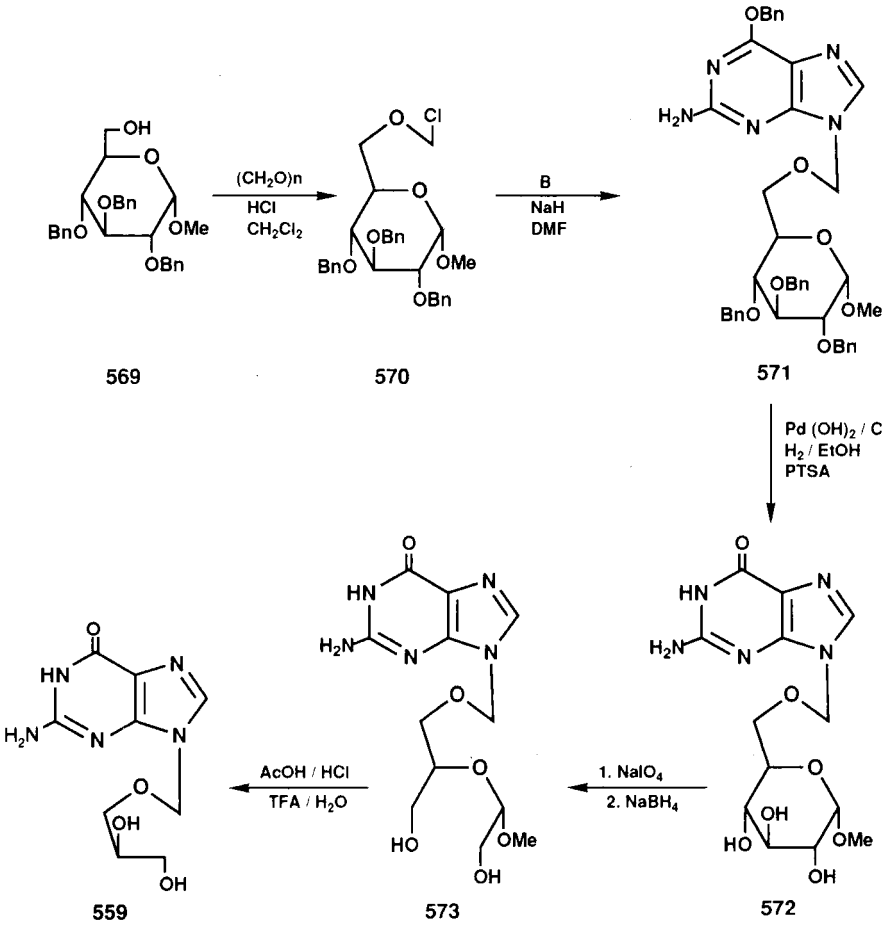


SCHEME 106

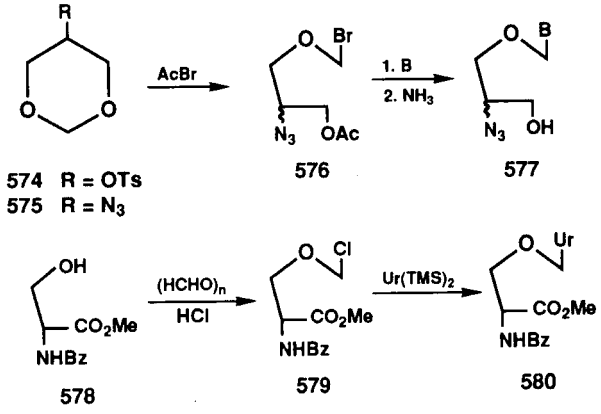
Reaction of the chloromethyl derivative **581** with a uracil derivative gave a mixture of **582** and **583** (91KFZ44).

3. *Deoxy and Branched-Chain Analogs*

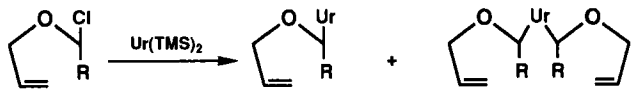
Selective benzoylation of the triol **584** gave **585,** whose acetoxymethyl ether **586** condensed with diacetylguanine in the presence of bis(*p*-nitrophenyl) phosphate and sulfolane to give **587,** which upon deprotection gave **588** (86JMC1384). Another precursor for branched-chain nucleosides was pentaerythritol triacetate **589,** which upon chloromethylation gave **590.** Condensation of **590** with 6-chloropurine or *N*-acetylguanine gave a mixture



SCHEME 107



SCHEME 108



581 582 583

SCHEME 109

of the 7- and 9-isomers, whose deprotection gave **591.** The pyrimidine analogs were prepared from the silylated pyrimidine (84MI5). All showed activity against herpes viruses.

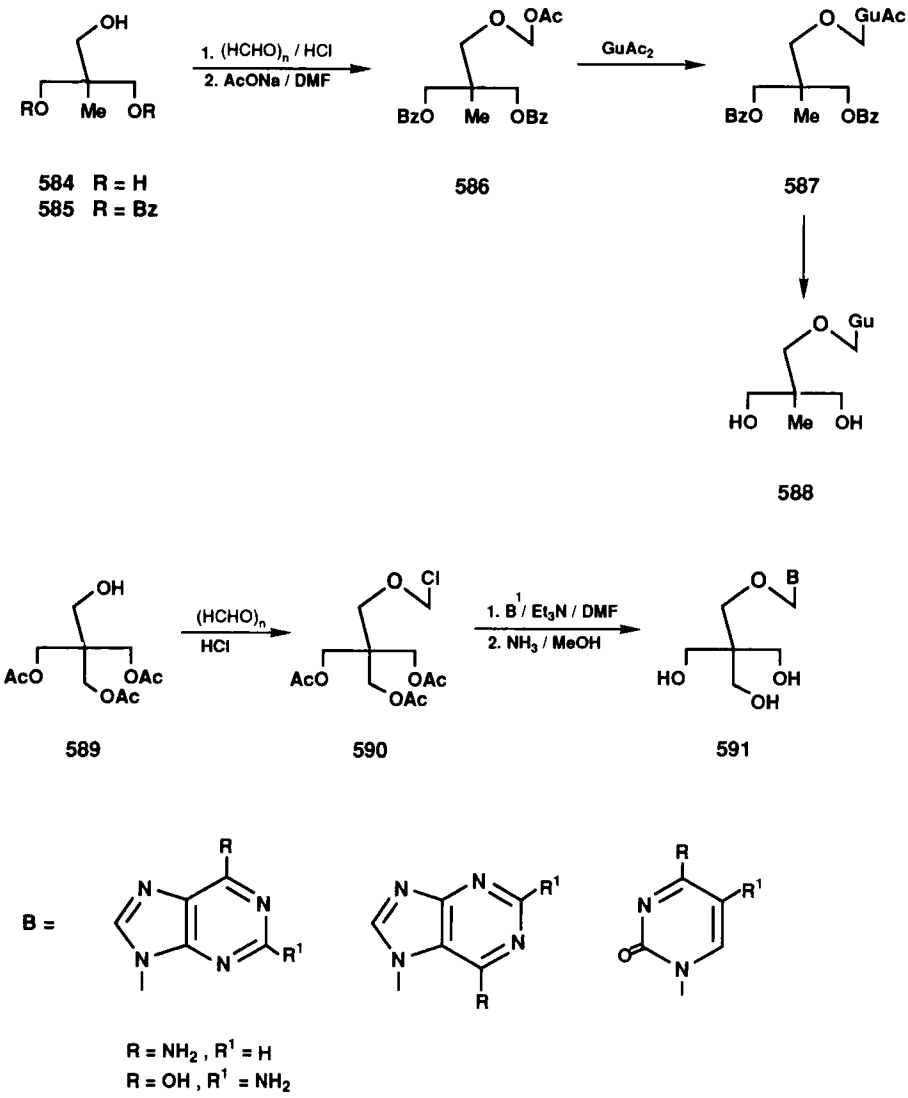
4. *Acyclo-C-Nucleoside Analogs*

The *C*-nucleoside analogs were prepared when 5-hydroxylmethyluracil **592** and glycerine were condensed in the presence of HCl to give **593,** whose methylation with DMF–dimethylacetal gave **595.** Further reaction with guanidine gave the isocytidine analog **597,** which was purified via its acetyl derivative **596.** In contrast, methylation of **593** with HMDS/MeI gave **594,** whose separation was achieved *via* acetylation and deacetylation (86JHC1621).

Acyclic analogs of pyrazofurin were prepared by heating **422** with alcohol **598** in the presence of sodium acetate followed by deprotection and amidation to give **599.** The respective 3′-deoxy analog was also prepared from the respective alcohol and exhibited slight activity against human cytomegalovirus (91MI4).

5. *Translocation of the Oxygen with Carbon Analogs*

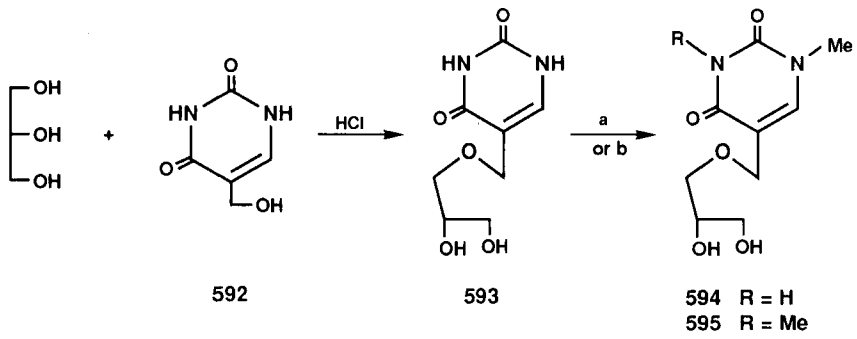
Translocation of the oxygen side chain with one of the two adjacent carbons could lead to two isomeric structures. Thus, nucleosides with C-1′ translocated with the oxygen of the side chain have been synthesized. The need for protecting groups was obviated by introducing the hydroxy functionalities of the acyclic substituent at a later stage in the synthesis, by hydroxylation of an exocyclic double bond. Thus, cyclization of unsaturated ureas **600** gave the pyrimidines **602,** which, on treatment with osmium tetroxide and *N*-methylmorpholine *N*-oxide in aqueous acetone, gave the acyclonucleosides **603** [90JCS(P1)2175]. The guanine acyclonucleosides having 2,3-dihydroxybutoxy side chains were prepared via the alkenoxy amines **601** by condensation with 4,6-dichloro-2,5-diformamidopyrimidine to give **604.** Closure of the imidazole ring was achieved by heating with diethoxymethyl acetate followed by treatment with ammonia and *cis*-



SCHEME 110

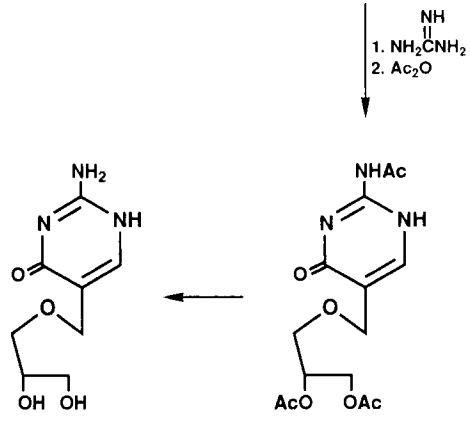
hydroxylation to give **605,** which upon treatment with formic acid gave **607** and upon catalytic hydrogenation gave **606.** Treatment of **605** with sodium methoxide gave the 4-methoxy derivative (91JMC57).

Nucleosides with a translocation of the oxygen with C-4′ were prepared by coupling of the chloroacetate **608** with various bases, followed by depro-



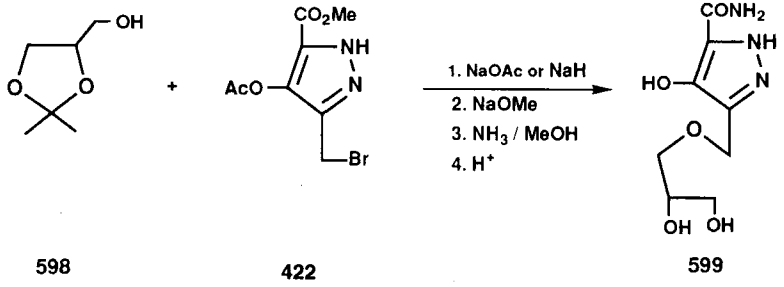
592 593 594 R = H
595 R = Me

a = HMDS, MeI; b= DMFDMA



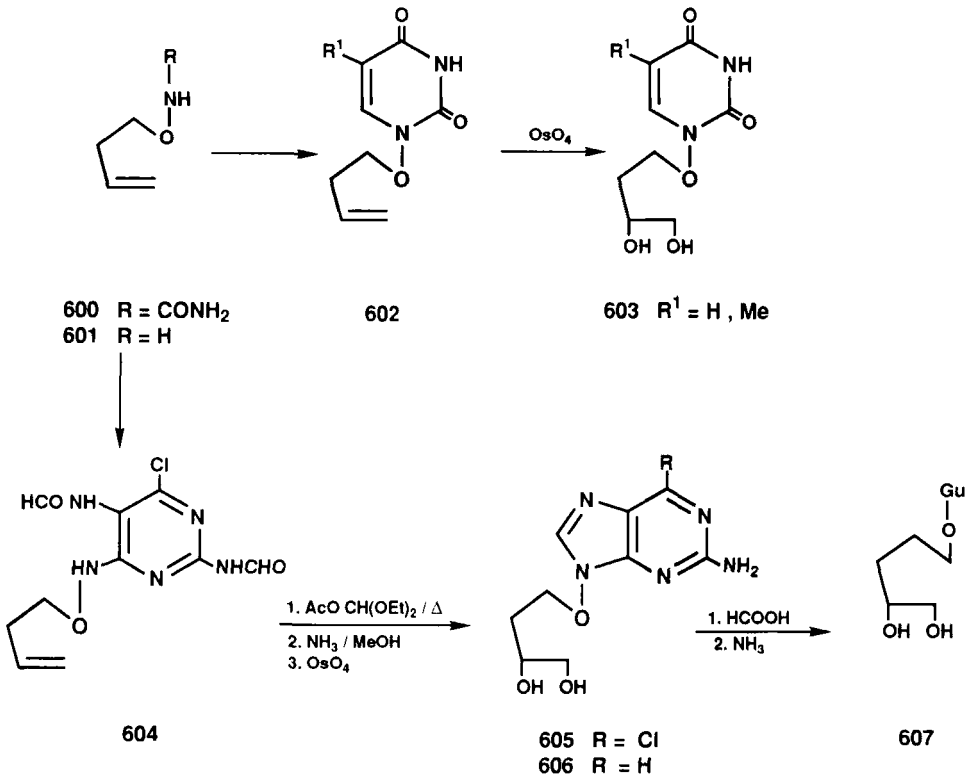
597 596

SCHEME 111



598 422 599

SCHEME 112



SCHEME 113

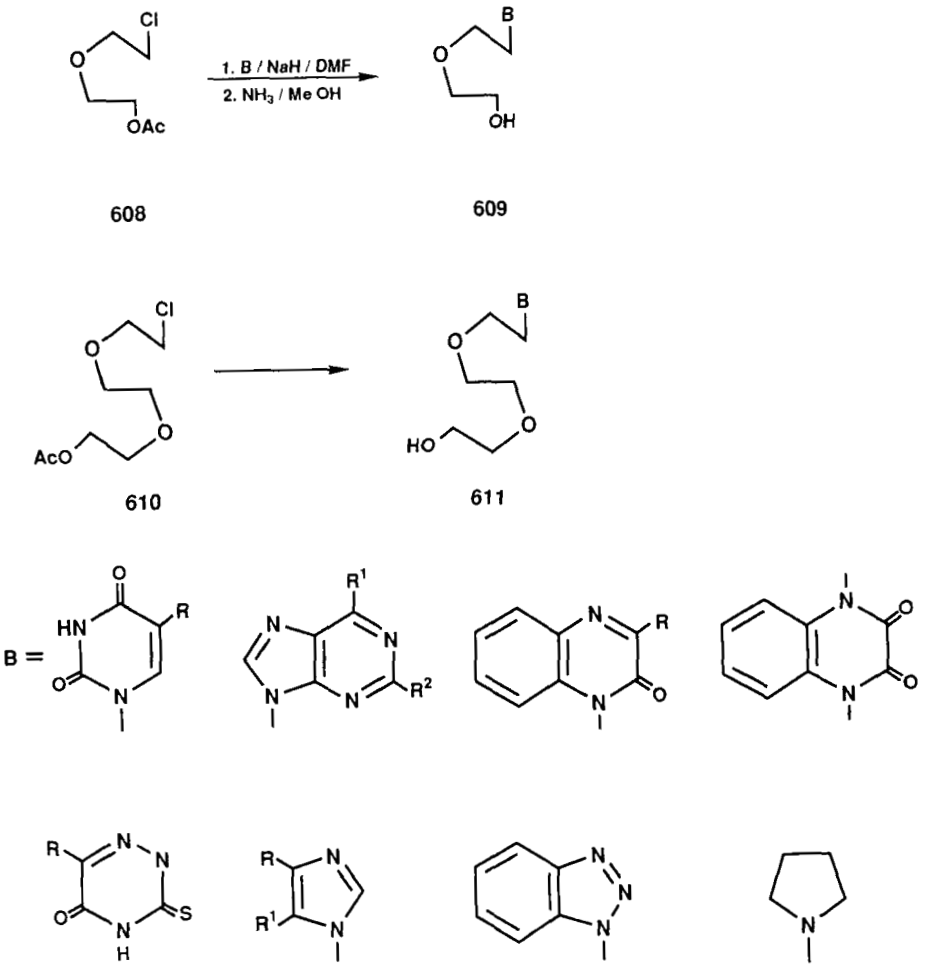
tection to give **609.** Similarly, the respective ethers **611** were prepared from **610** (89CS379; 96UP1).

C. 2′,3′- AND 3′,4′-*diseco*-NUCLEOSIDES (TYPE 2.3)

1. *General Methods for Construction*

Debenzoylation of the nucleoside analogs **612** gave **613,** which upon periodate oxidation and reduction gave the optically pure enantiomers **614.** Similarly, uracil analog **615** gave also the corresponding **614** (88KGS223).

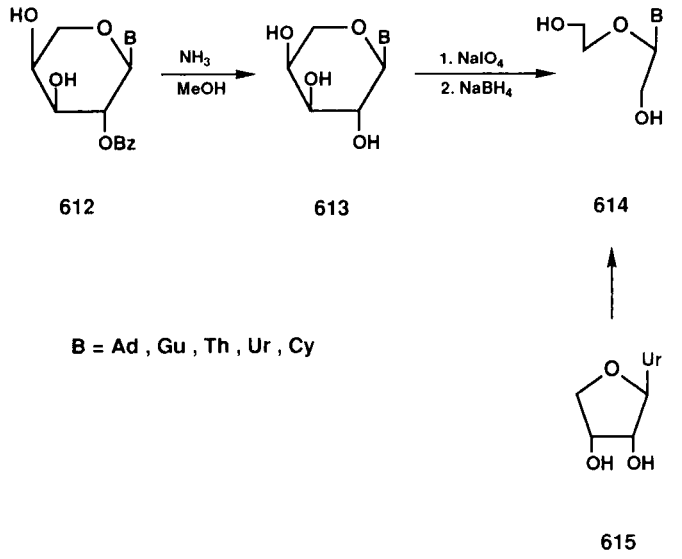
The racemic analogue **620** was prepared by alkylation of *N*-2,9-diacetylguanine with 2,3-dichlorotetrahydrofuran **616.** The adduct **617** was deacetylated to give **618,** and then monomethoxytritylated followed by



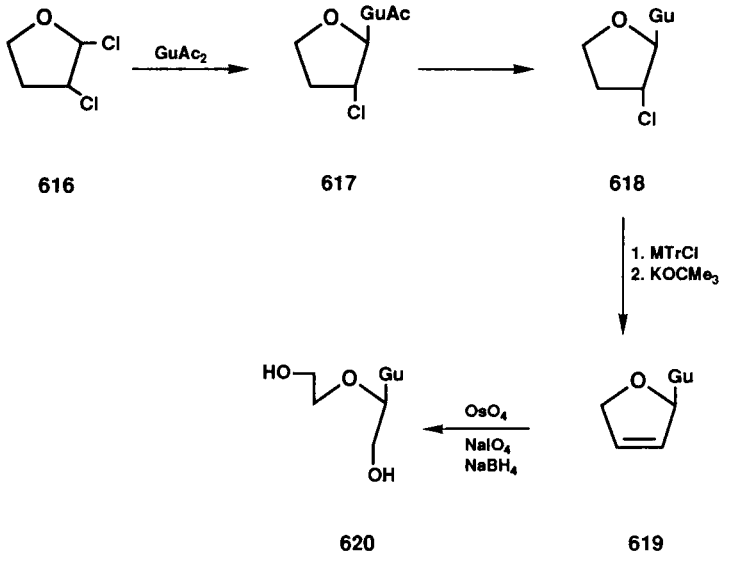
SCHEME 114

elimination of HCl to give **619.** Treatment of **619** with OsO_4–$NaIO_4$ and then reduction gave **620** (86CJC1885).

The racemic analogs were also obtained by replacement of the halogen atom in 2-chloromethyldioxolane **622,** obtained from ethylene glycol and **621,** by an acetoxy group to give **623.** Subsequent opening of the dioxolane ring with acetic anhydride in presence of $ZnCl_2$ gave **624,** followed by reaction with the base to give **625.** 1-Alkyl derivatives were almost the only product of the alkylation of trimethylsilyl derivatives of pyrimidine bases,



SCHEME 115



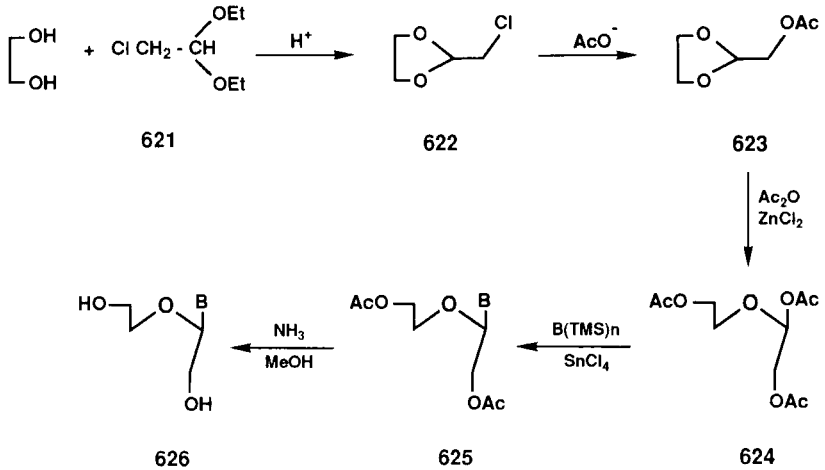
SCHEME 116

whereas a mixture of the 9- and 7-substituted isomers was formed in the case of 6-*N*-benzoyladenine. Treatment of the protected analogs with a methanolic solution of ammonia led to **626** (88KGS223).

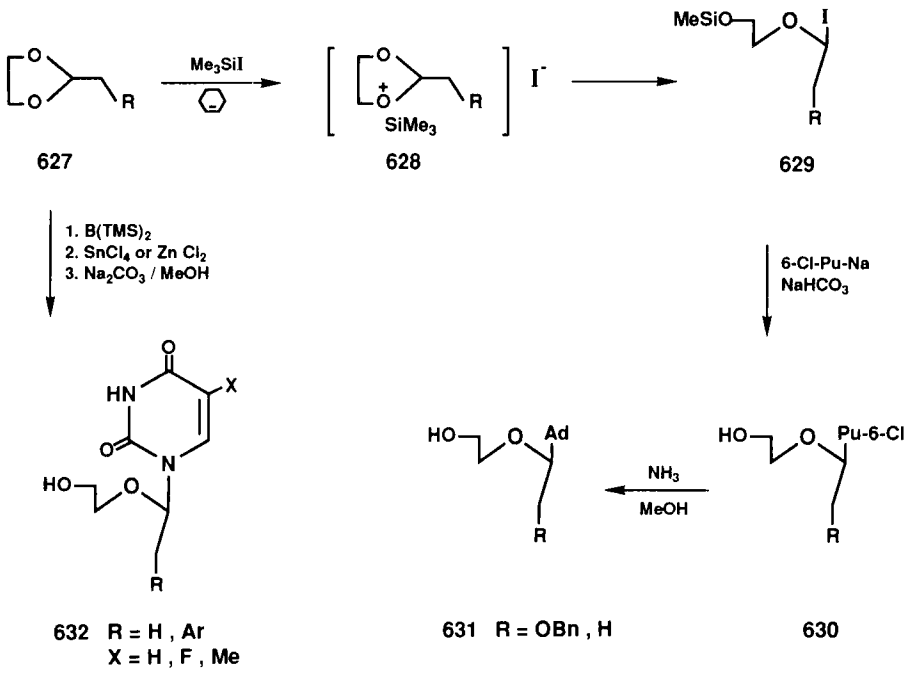
Alternatively, ring opening of various 2-substituted dioxolanes **627** with trimethylsilyl iodide provided acyclic sugar analogs **629,** via **628;** these are lacking only C-3′. Coupling with the sodium salt of 6-chloropurine gave **630,** whose reaction with NH_3 gave **631** (79JOC3733). Other pyrimidine analogs **632** were also prepared from 1,3-dioxolanes **627** by treatment with base in the presence of a Lewis acid (anhydrous stannic chloride or zinc chloride) in an inert solvent under similar conditions to those of the modified Hilbert–Johnson method. This was followed with methanol containing sodium hydrogen carbonate or aqueous sodium hydroxide to give *N*-1-substituted pyrimidine (uracil) acyclonucleosides **632** and a minor product of the respective *N*-1,*N*-3-bis-substituted derivatives (85CPB1703).

2. *Modified Side-Chain Analogs*

The syntheses of di- and trifluoromethyl acyclonucleosides **634** are based on the substitution of the mesylates of the corresponding hemiacetals **633,** obtained by condensing ethylene glycol monobenzyl ether with di- or trifluoroacetaldehyde followed by mesylation. Their substitution by 2-amino-6-chloropurine or N^4-acetylcytosine gave **634,** followed by hydrolysis and then hydrogenolysis (91TL3823). They were less active than acyclovir.



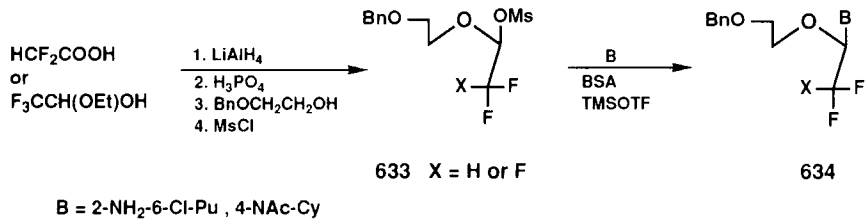
SCHEME 117



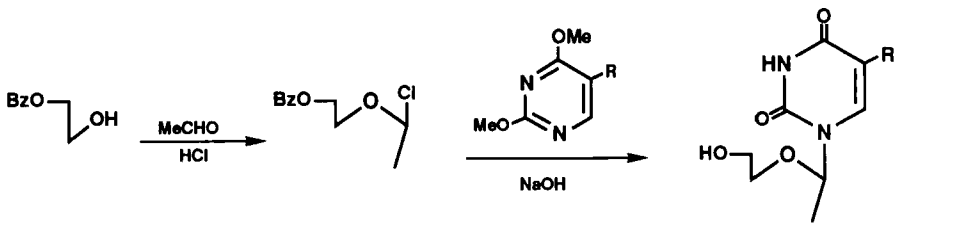
SCHEME 118

Reacting ethylene glycol monobenzoate **635** with acetaldehyde and HCl gas gave **636,** whose reaction with pyrimidine derivatives followed by debenzoylation gave **637** (86JHC1651). The base-catalyzed hydrolysis of 6-substituted 9-(1-ethoxyethyl)purines takes place by nucleophilic attack of hydroxyl ion on C-8 of the purine moiety [82ACSA(B)707].

Condensation of 2-(benzyloxy)ethanol with a mixture of the hydrate and methyl hemiacetal of methyl glyoxalete **638** gave a hemiacetal, which was converted directly with methanesulfonyl chloride to α-chloro ether **639.** It condensed with silylated uracil, 5-fluorouracil, and N^4-acetylcytosine,

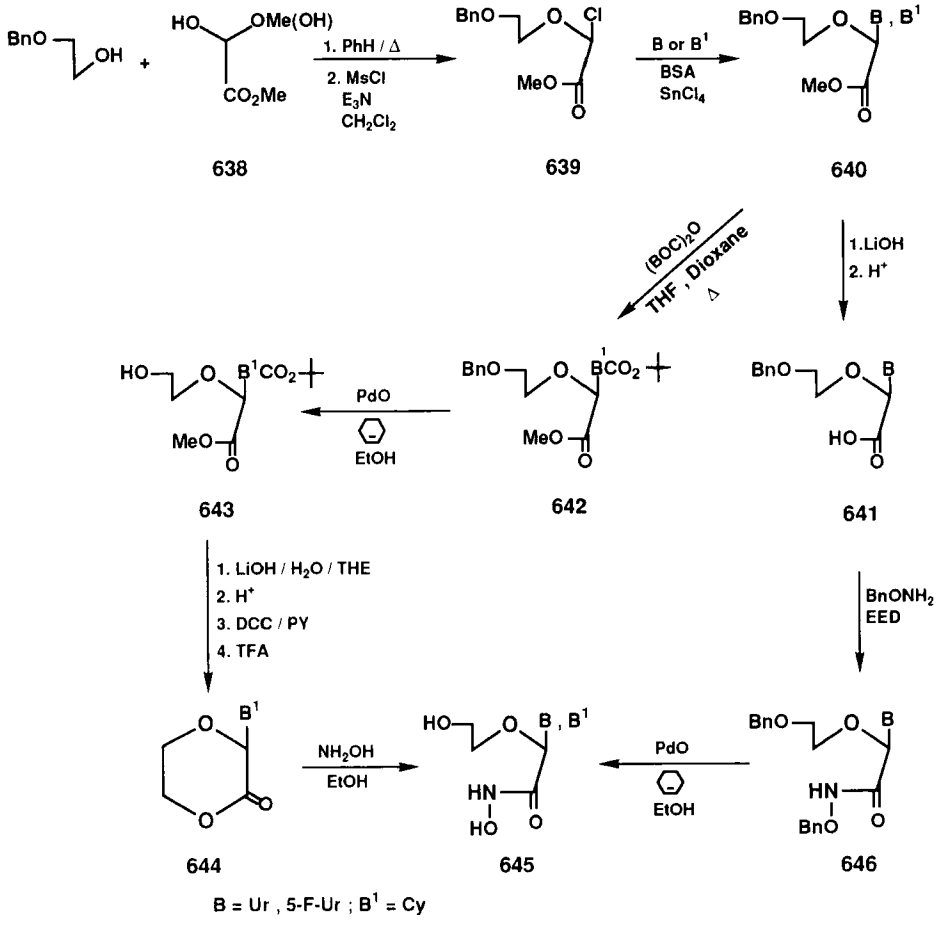


SCHEME 119



635 636 637 R = Bn , $BnOC_6H_4CH_2$

SCHEME 120

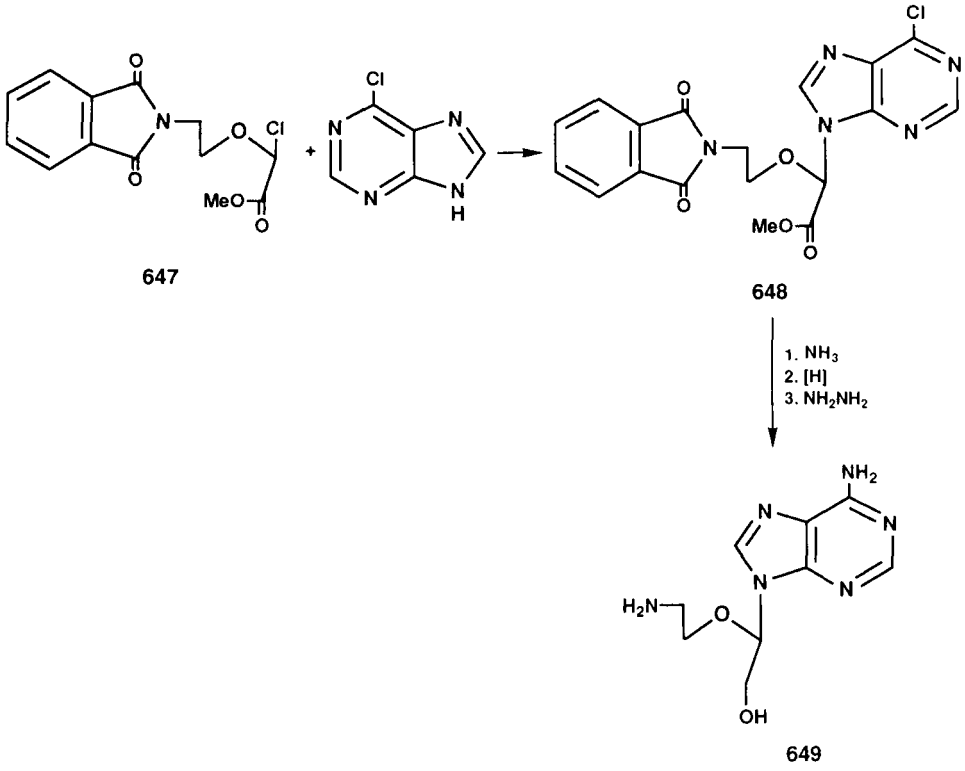


B = Ur , 5-F-Ur ; B^1 = Cy

SCHEME 121

generated *in situ* from the bases and *N,O*-bis(trimethylsilyl)acetamide (BSA), in presence of stannic chloride to give pyrimidine acyclonucleosides **640.** Reaction of the ester with NH_2OH was unsuccessful. Therefore, the esters were saponified to the corresponding acids **641** and then coupled to *O*-benzylhydroxylamine to give **646.** Didebenzylation of a uracil derivative was smoothly accomplished with PdO-catalyzed transfer hydrogenation. However, the 5-fluoro derivative could not be obtained in sufficient purity. This problem required the development of a mild method generating the hydroxamic acid as the final step in the synthesis. Lactones seemed ideally suited for this purpose. Catalytic transfer hydrogenation of **642** gave **643;** this, upon lactonization, gave **644,** which reacted with NH_2OH to give **645.** The hydroxamates inhibited CDP reductase activity (89JMC1879).

The ring-opened analog of 5′-aminocordycepin was prepared by reaction of 6-chloropurine with phthalamide **647** to give **648,** which upon conversion of the chloro substituent to amine, reduction of the ester group, and hydrazinolysis gave **649** (87MI1).



647 648 649

SCHEME 122

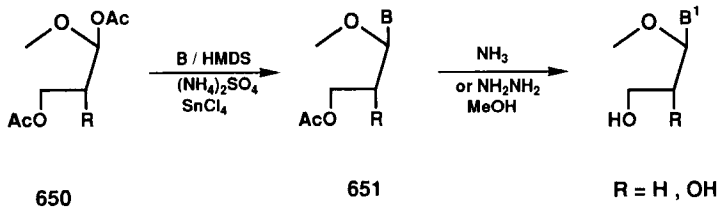
D. 3′,4′- AND 4′,5′-*diseco*-NUCLEOSIDES (TYPE 2.4)

1. *Typical Examples*

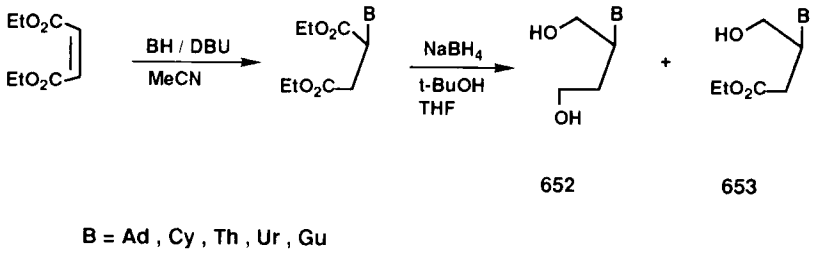
Reaction of 2,3-diacetoxy-1,1-dimethoxypropane and 1,3-diacetoxy-1-methoxypropane **650** with bis-*O*-trimethylsilyluracils and *N,O*-bis-trimethylsilyl-*N*-acetylcytosine in the presence of stannic chloride, a modification of the Helbert–Johnson reaction, gave **651.** Also, 2,3-divaleryloxy-1,1-dimethoxypropane was used (85MI6). Similarly, reaction of pertrimethylsilyl derivatives of *N*-benzoyladenine with 1,2,3-triacetoxy-1-methoxypropane gave N-9 and N-7 isomers, whereas the reaction with 1,3-diacetoxy-1-methoxypropane afforded the N-9 isomer (87MI3). Nucleoside analogs of 2-*N*-acetylguanine, hypoxanthine, and diacetamide purine were also prepared (87MI3). Acetyl groups were subsequently removed from most of the protected analogs by treatment with ammonia in aqueous methanol, except in the case of 5-trifluoromethyluracil, which gave the 5-cyano derivative. Because fluoride ion is normally a poor leaving group in displacement and elimination reactions, direct displacement of fluoride by ammonia seemed unlikely, and a more plausible mechanism for this transformation involved initial attack of ammonia at C-6. 2,3-Bis(trimethylsilyloxy)-1,1-dimethoxypropane was used where subsequent removal of the *O*-trimethylsilyl groups under neutral aqueous conditions was required. Under the reaction conditions employed, condensation of bis-*O*-trimethylsilyl-5-nitrouracil and *N,O*-bis-trimethylsilyl-*N*-acetylcytosine with 1,3-diacetoxy-1-methoxypropane afforded, not only the 1-N alkylated products, but also the 1,3-disubstituted pyrimidines. The activity of these acyclonucleosides was studied toward influenza A, parainfluenza type 1, and herpes simplex type 1 viruses.

2. *Carboacyclic Analogs*

Michael addition of nucleobases to diethyl maleate followed by reduction gave **652** and **653** (92MI6). The uracil analog exhibited only marginal activity against HIV.

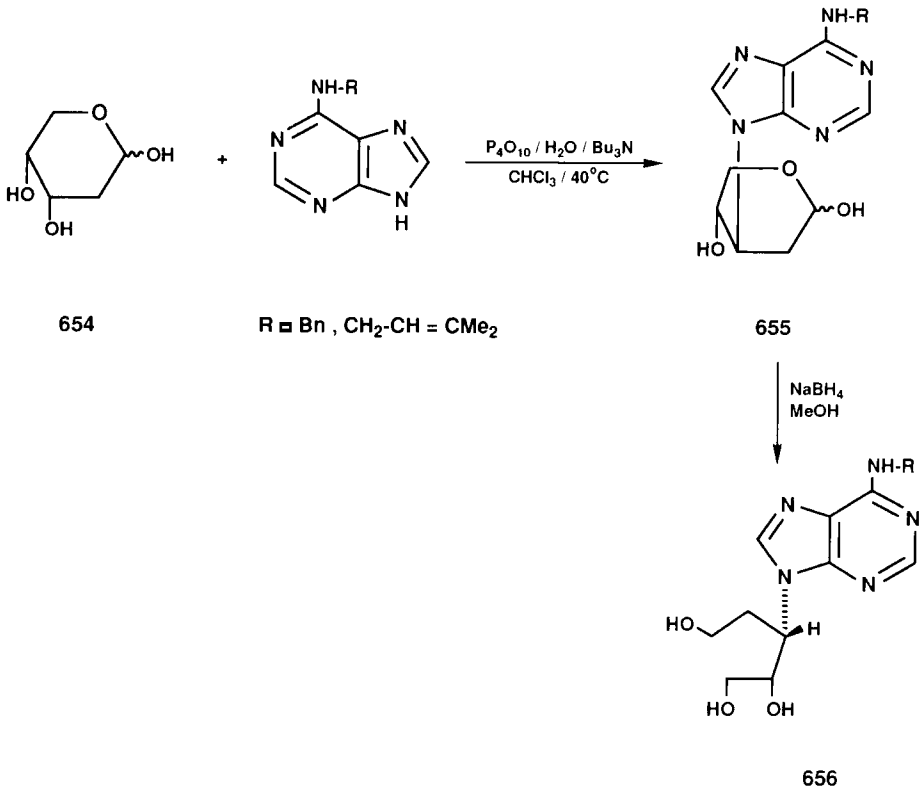


SCHEME 123



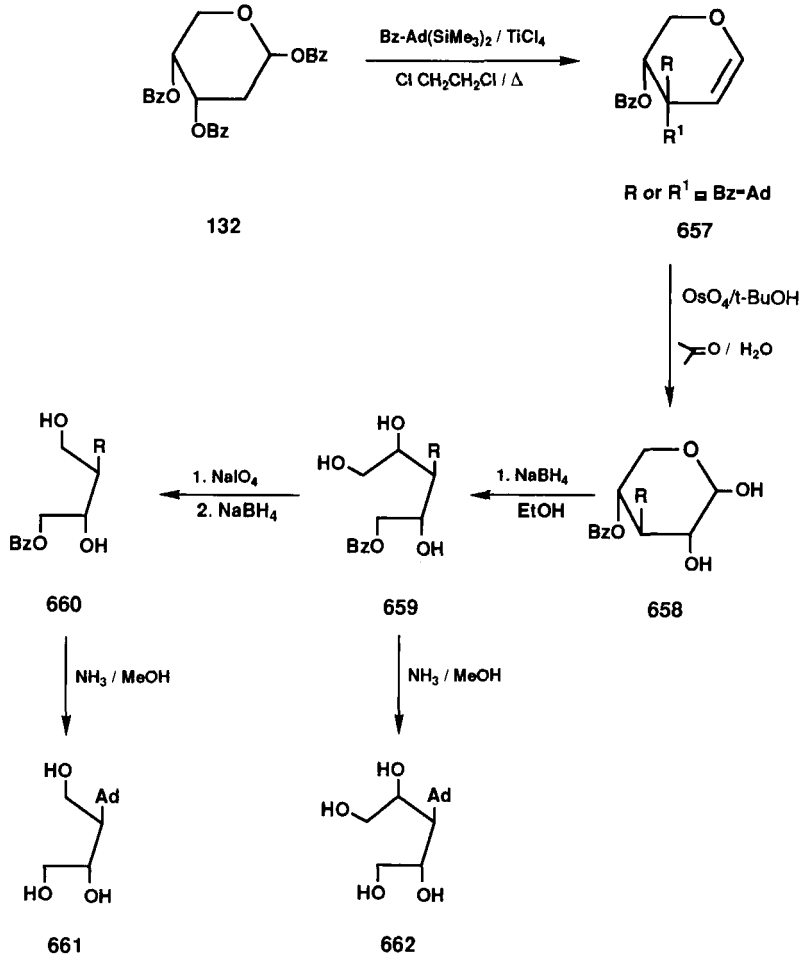
SCHEME 124

Condensation of *N*-alkyladenine with 2-deoxyribose (**654**) in a phosphorus pentoxide mixture gave **655** via a probable Michael-type addition to an α,β-unsaturated sugar aldehyde formed *in situ* from 2-deoxyribose. Reduction of **655** gave **656** (92JHC511). Neither **655** nor **656** showed any significant activity against HSV-1.



SCHEME 125

Reaction of 1,3,4-tri-*O*-benzoyl-2-deoxy-D-ribofuranose (**132**) with the silyl derivative of benzoyladenine in the presence of $TiCl_4$ gave a mixture of **657.** They were also formed by reaction of the respective 1-chlorosugar with the adenine derivative. The high reactivity of the sugar derivative resulted in a facile elimination of hydrogen chloride. *Cis*-hydroxylation of one of the isomers of **657** gave an anomeric mixture of **658,** whose reduction gave **659;** a migration of the benzoyl group had taken place. Debenzoylation of **659** gave **662,** whereas its periodate oxidation and reduction gave **660,** which upon debenzoylation gave **661** (91T9993).

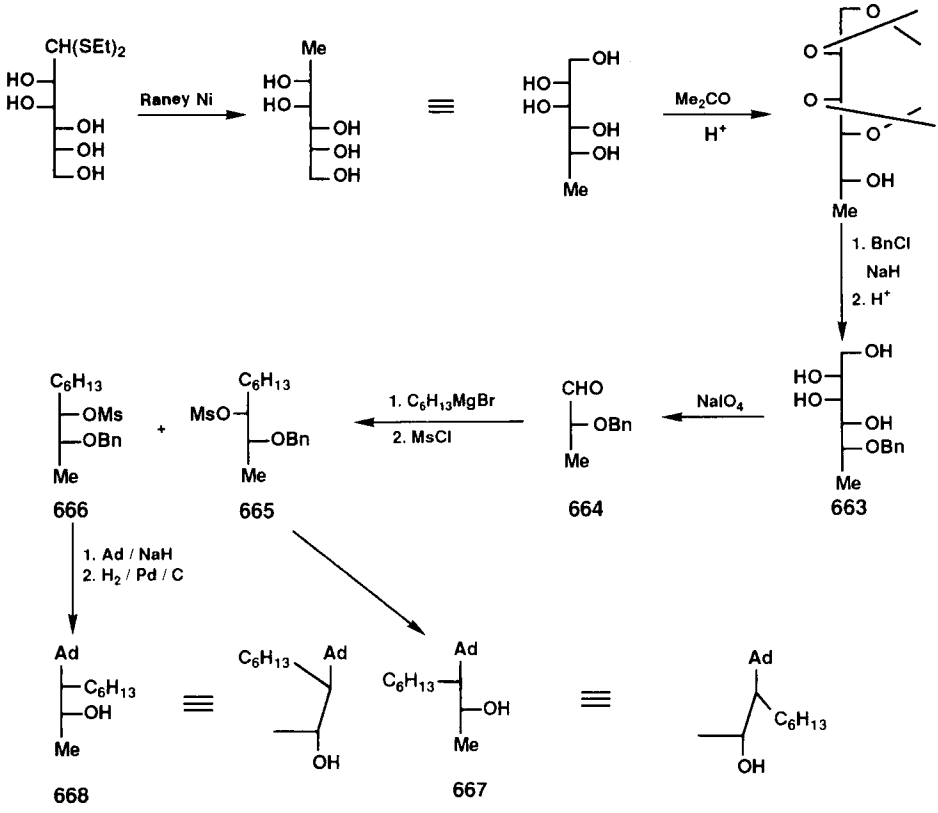


132 657 658 659 660 661 662

SCHEME 126

3. *EHNA Analogs*

The acyclicnucleoside *erythro*-9(2-hydroxy-3-nonyl)adenine (74JMC6; 78MI1) is abbreviated as EHNA. Because of its importance as an inhibitor of adenosine deaminase, various approaches were reported for the synthesis of the chiral isomers (81JMC1383, 81MI1; 82JOC2179, 82MI2; 88JMC390). Thus, the synthesis of both isomers of EHNA from D- and L-rhamnose was reported (82JOC2179). Scheme 127 depicts those derived from D-rhamnitol. The key intermediate *R*-2-(benzyloxy)propanal (**664**) derived from 5-*O*-benzyl-D-rhamnitol (**663**) was condensed with hexylmagnesium bromide to give a 3:1 mixture of threo/erythro alcohols. Both were converted to the respective mesylated products **665** and **666,** whose displacement with (adenin-9-yl) sodium salt gave the erythro **667** and threo **668** isomers of EHNA, respectively. A similar sequence was also depicted for the other two isomers from L-rhamnitol.



SCHEME 127

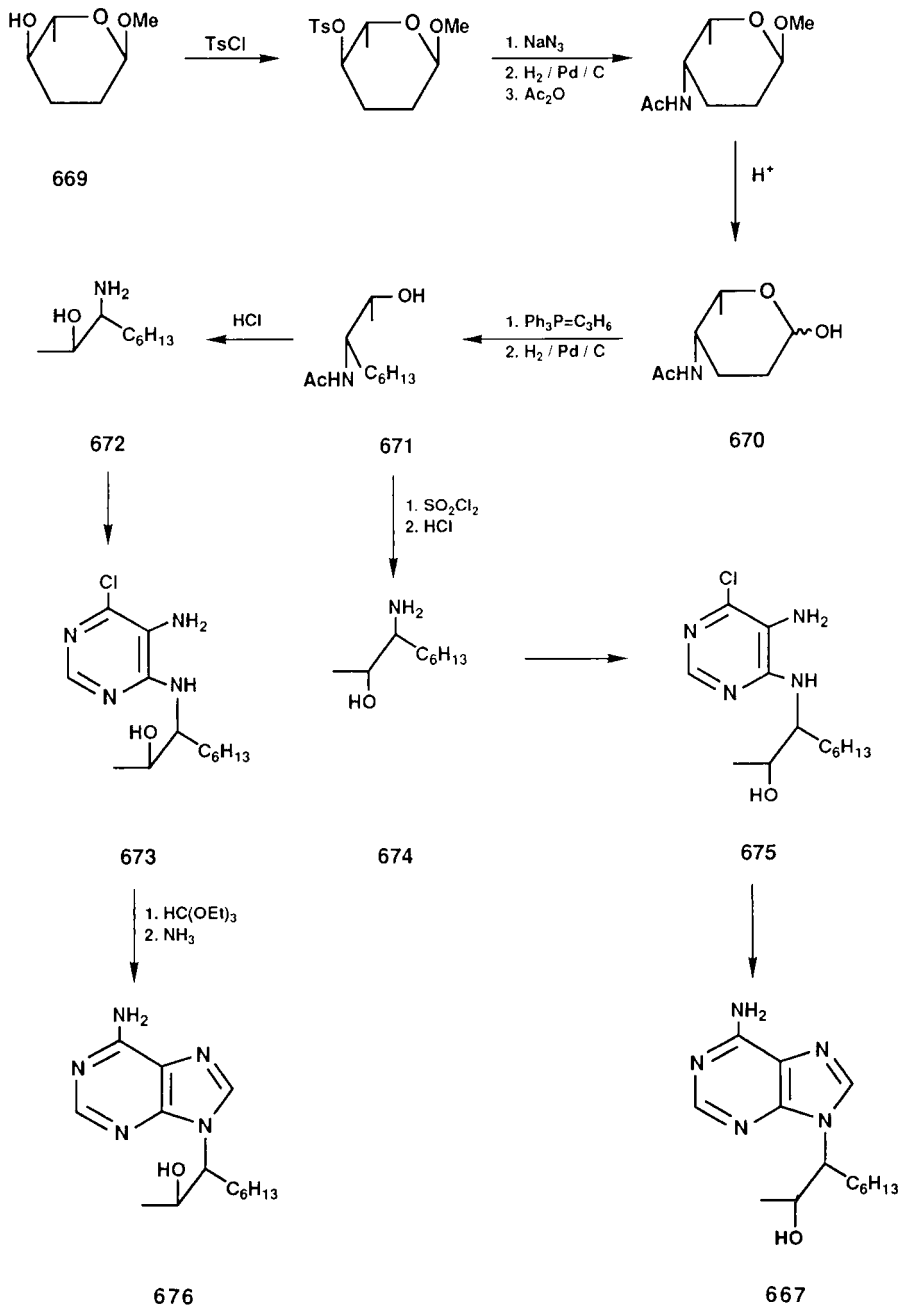
Alternatively, the heterocyclic ring was built onto an amino alcohol precursor that is derived from the sugar precursor methyl-L-amicetoside (**669**), obtained from L-rhamnose, by tosylation followed by azide displacement, reduction, acetylation, and then hydrolysis to give **670.** Reaction of **670** with a Wittig reagent gave the acetylamino alcohol **671,** whose hydrolysis with HCl gave the *threo*-aminoalcohol (2*S*,3*S*)-**672.** However, treatment with thionyl chloride prior to hydrolysis with HCl resulted in the inversion of configuration of C-2 by an S_N1 mechanism, involving an oxazoline intermediate to provide the erythro isomer (2*R*,3*S*)-**674.** The other two isomers could be prepared from methyl α-rhodinoside, obtained from **669** by an inversion of configuration at C-4, by a similar sequence of reactions on **669** shown in Scheme 128 (81JMC1383). The amino alcohols were converted to their respective adenine analogs by condensation with 5-amino-4,6-dichloropyrimidine to give **673** and **675,** which was followed by cyclization and reaction with ammonia to give **676** and **667,** respectively (74JMC6).

The chiral aminoalcohol precursor for the synthesis of EHNA analogs could be obtained from L-ascorbic acid, whose isopropylidenation gave **677,** which was transformed via degradation and esterification to **678** (84TL3841). Reduction of **678** followed by tosylation and epoxide formation gave **679.** Addition of pentylmagnesium chloride followed by mesylation gave **680,** whose azide displacement and reduction gave **681.** Further conversion to the 3-deaza analog **685** was achieved via **682.** Conversion of **681** to **684** was also achieved via **683.** Reductive periodate cleavage of **684** gave **686,** which was converted to the fluoro analog by treatment with DAST. In contrast, the respective chloro and bromo derivatives were prepared via the corresponding tosylate by treatment with Bu_4NX.

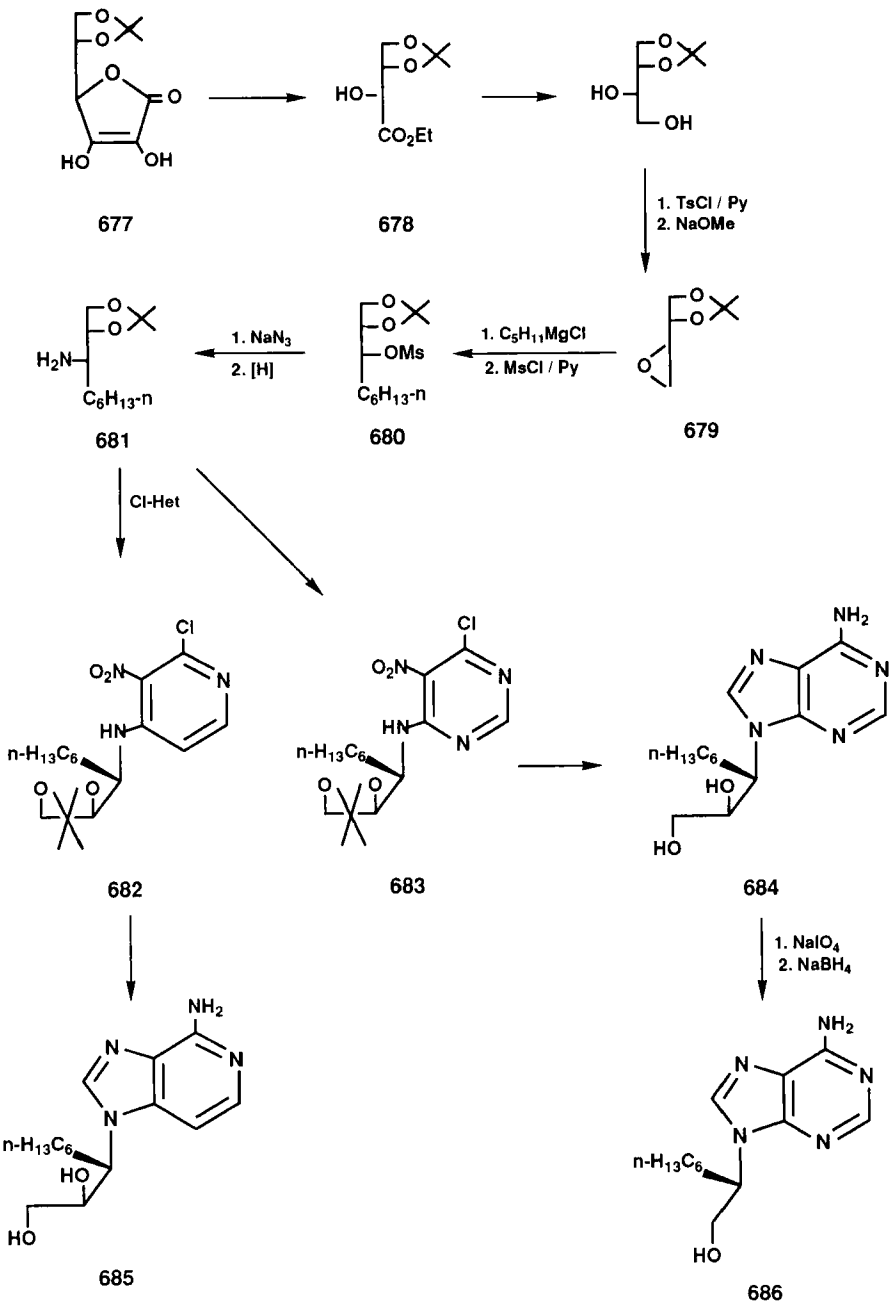
The erythro isomer could also be prepared from **679.** Thus, reduction of **679** followed by benzylation and then hydrolysis gave **687,** whose tosylation and treatment with base gave the respective epoxide, which upon addition of 1-pentenyl-5-magnesium bromide gave **688.** Conversion of the alcoholic group in **688** to an amino group was achieved by a Mitsunobu reaction to the azido group followed by reduction. Amination of the chloroheterocycle followed by reduction and cyclization gave **689.** Amination, hydroboration, and debenzylation then gave **690.**

The 7-deaza EHNA analog **691** was obtained by condensation of 4,6-dichloropyrimidine-5-acetaldehyde with **674.** The 1,3-dideaza EHNA analog was prepared from erythro-3-amino-2-nonanol (**674**) by condensation with 1-chloro-2,3-dinitrobenzene, prepared in turn from 1-amino-2,3-dinitrobenzene, to give **692.** Reduction followed by cyclization with formamidine acetate gave **693** (88JMC390).

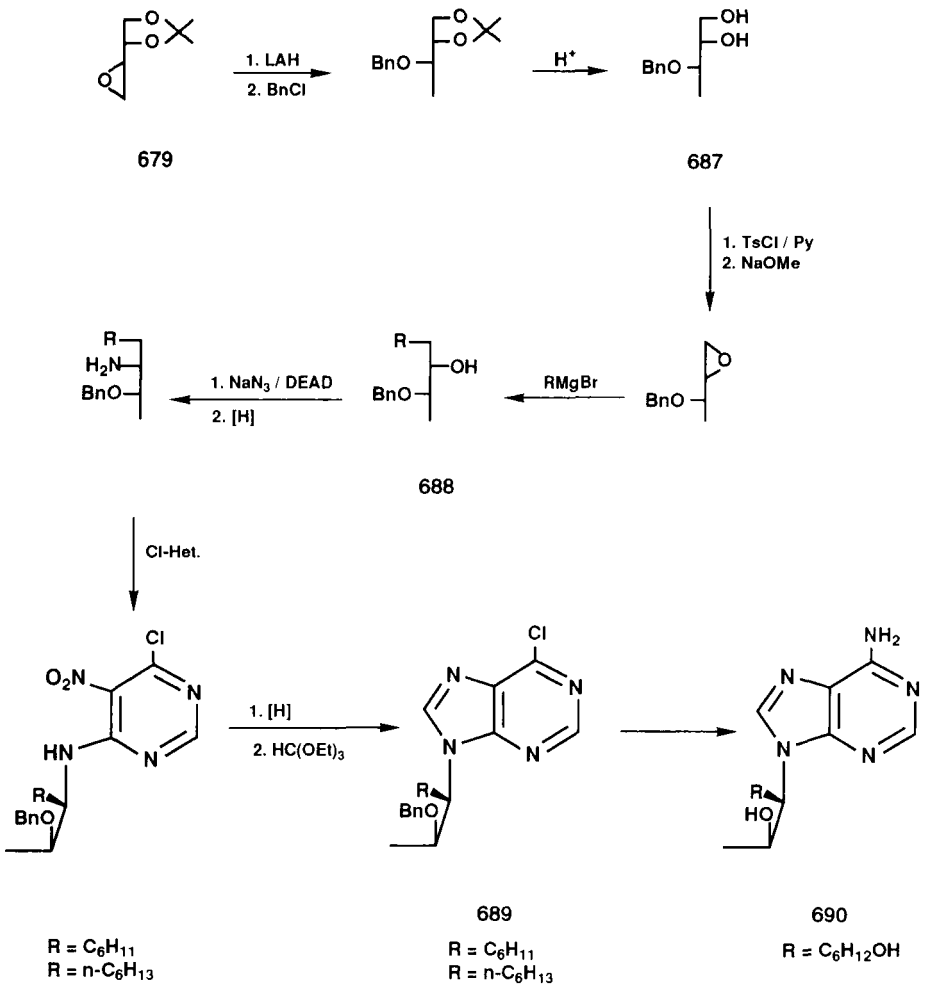
As a further modification of EHNA, condensation of ethyl-2-amino-2-cyanoacetate or aminomalononitrile with erythro-3-amino-2-nonanol in


HO
O
OMe
TsCl
TsO
1. NaN3
2. H2 / Pd / C
3. Ac2O
AcHN
669
H+
OH
1. Ph3P=C3H6
2. H2 / Pd / C
HCl
NH2
C6H13
672
671
670
1. SO2Cl2
2. HCl
Cl
N
NH
673
674
675
1. HC(OEt)3
2. NH3
676
667

SCHEME 128


677
678
1. TsCl / Py
2. NaOMe
679
1. $C_5H_{11}MgCl$
2. MsCl / Py
680
1. NaN_3
2. [H]
681
Cl-Het
682
683
684
1. $NaIO_4$
2. $NaBH_4$
685
686

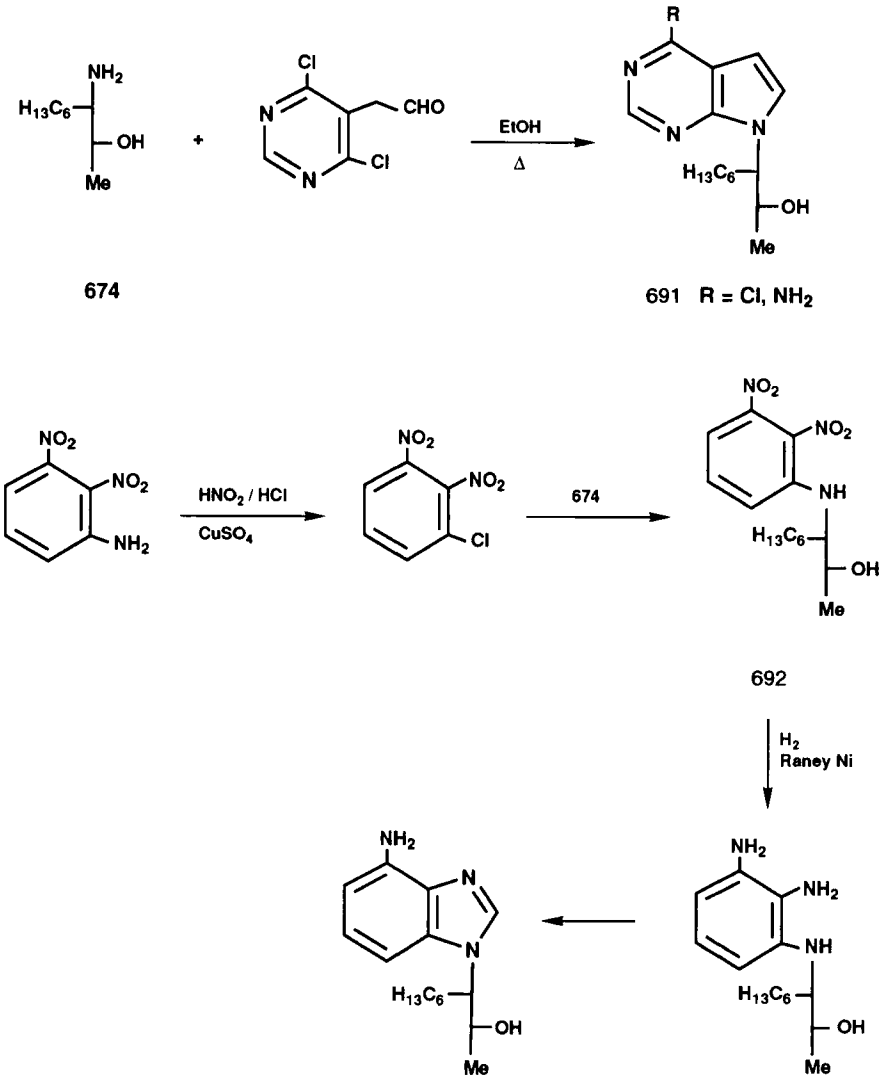
SCHEME 129



SCHEME 130

presence of triethyl orthoformate gave imidazole derivatives. Chemical modification of the two substituents afforded a variety of analogs (91JMC1187).

EHNA in its racemic form was designed as a semitight binding inhibitor of ADA. The synthesis of the chiral isomers allowed identification of the (+)2*S*,3*R* as the most potent ADA inhibitor. This led to enhancement of ara-A activity against human pancreatic and colon carcinomas. (+)EHNA has a short duration of action, and it is believed to be metabo-


NH2
H13C6
OH
Me
674
Cl
CHO
N
Cl
EtOH
Δ
R
691 R = Cl, NH2
NO2
NH2
HNO2 / HCl
CuSO4
Cl
674
NH
692
H2
Raney Ni
693

SCHEME 131

lized by a cytochrome P-450 mediated hydroxylation in the nonyl side chain. The 3-deaza(±)EHNA had comparable activity to (±)EHNA (84JMC274; 88JMC390). EHNA has the antineoplastic activity of adenosine analogs against human pancreatic DAN and human colon HCT-8 carcinomas (88MI1).

E. 4′,5′- AND 4′,*x*-*diseco*-NUCLEOSIDES (TYPE 2.5)

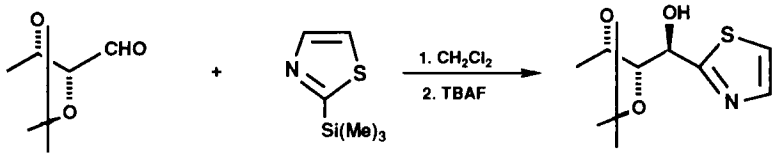
Although typical examples of this type are few, the respective 4′-hydroxylated analogs are frequently prepared. During work aiming to elongate the sugar chain, thiazole nucleoside **696** was prepared by an anti-diastereoselective addition of 2-trimethylsilylazoles (thiazole, benzothiazole, oxazole) **695** to asymmetric aldehydes **694** to give the corresponding *O*-silylcarbinoles in high stereoselectivity (85TL5477; 89JOC693).

Condensation of D-ribonolactone (**698**) with 2-(3,4-methylenedioxyphenyl)ethylamine (**697**) gave an amide **699,** whose acetylation with Ac_2O in pyridine and subsequent oxidation with *m*-chloroperbenzoic acid gave nitrone **700,** which was then hydrogenated in an acetic acid–HCl mixture over Adams catalyst and acetylated *in situ* to give **701** and **702** isolated by chromatography [92JCR(S)402].

The reaction of aminosugar **704** with isocyanates and isothiocyanates has been studied extensively (85AQ(C)147; 91MI2, 91MI3). The reaction gave **703** via the formation of a ureido derivative, which is too reactive to be isolated. The formation of **705** from **704** during the acetylation and deacetylation was studied.

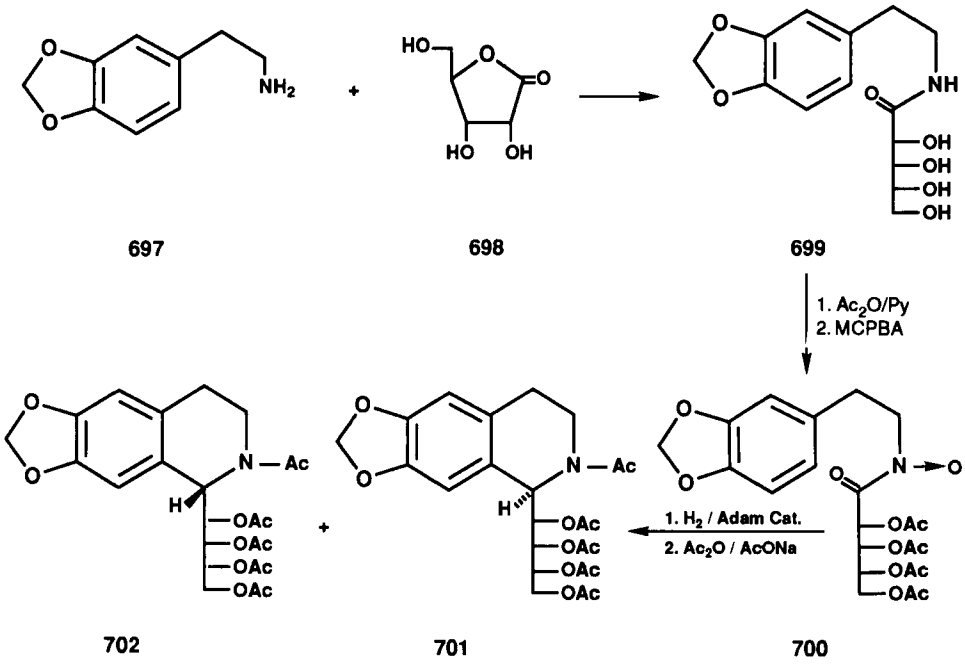
Reaction of 1-amino-1-deoxy-D-arabino hexulose **706** with cyanamide gave the imidazolin-2-ylideneammonium picrate **707** (89MI2).

The reaction of D-glucosamine **704** with 1,3-dicarbonyl compounds either in an acyclic structure or in a cyclic form gave **708** (84MI1; 85MI2; 92MI3).



694 **695** **696**

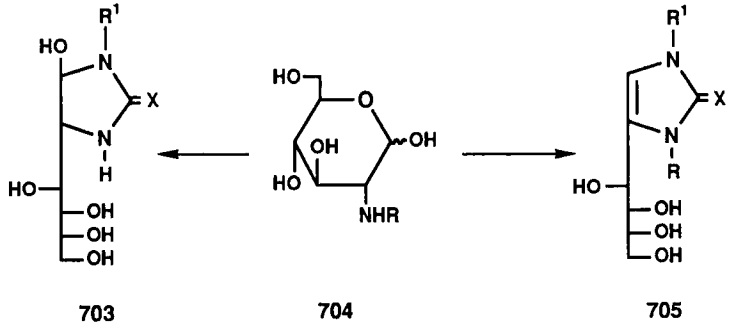
SCHEME 132



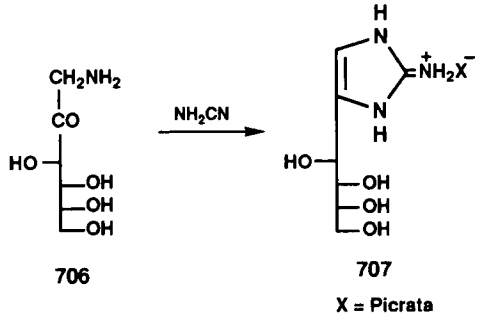
SCHEME 133

The 1,2,3-triazoles **710** readily obtained from osazones **709** could be reacted with HBr/AcOH to give **711** (96UP2).

Reaction of per-*O*-benzoyl aldononitriles **712** with ammonium azide gave the tetrazole benzoate **713,** whose debenzoylation gave **714.** Other analogs with a different configuration were also prepared (79MI1).



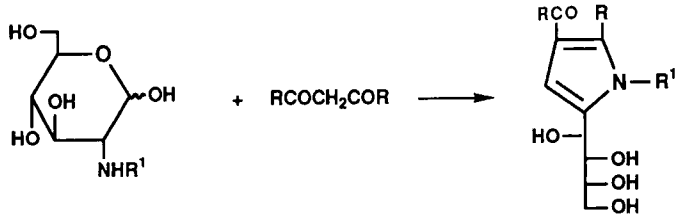
SCHEME 134



706 707

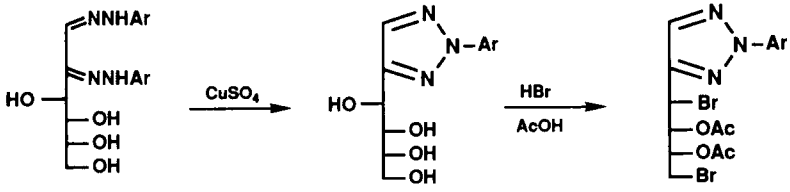
X = Picrata

SCHEME 135



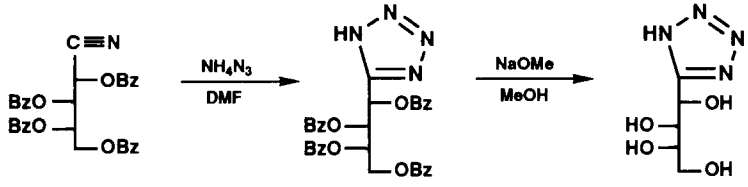
704 708

SCHEME 136



709 710 711

SCHEME 137



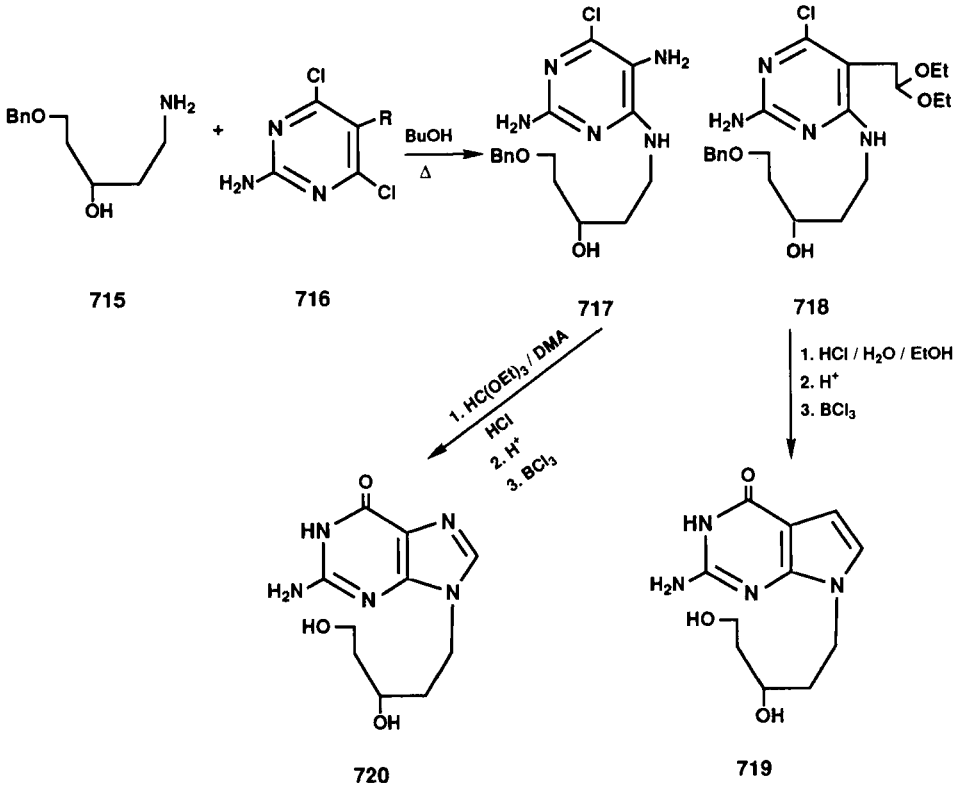
712 713 714

SCHEME 138

F. 1′,*x*- AND 4′,*x*-*diseco*-NUCLEOSIDES (TYPE 2.6)

The starting material was prepared by benzylation of but-3-en-1-ol followed by epoxidation with MCPBA to give an epoxide, whose ring opening was achieved with trimethylsilyl cyanide in the presence of diethylaluminium chloride to give a hydroxy nitrile derivative. Complete reduction of the nitrile with lithium aluminum hydride in diethyl ether led to **715,** which was condensed with 2-amino-4,6-dichloro-5-(substituted)pyrimidine (**716**) to produce **717** and **718,** depending on the substituent R. The latter, upon acidic hydrolysis and removal of the benzyl group, gave **719.** The synthesis of guanine analog **720** was achieved by cyclization of **717** followed by hydrolysis and deprotection (90JMC2476).

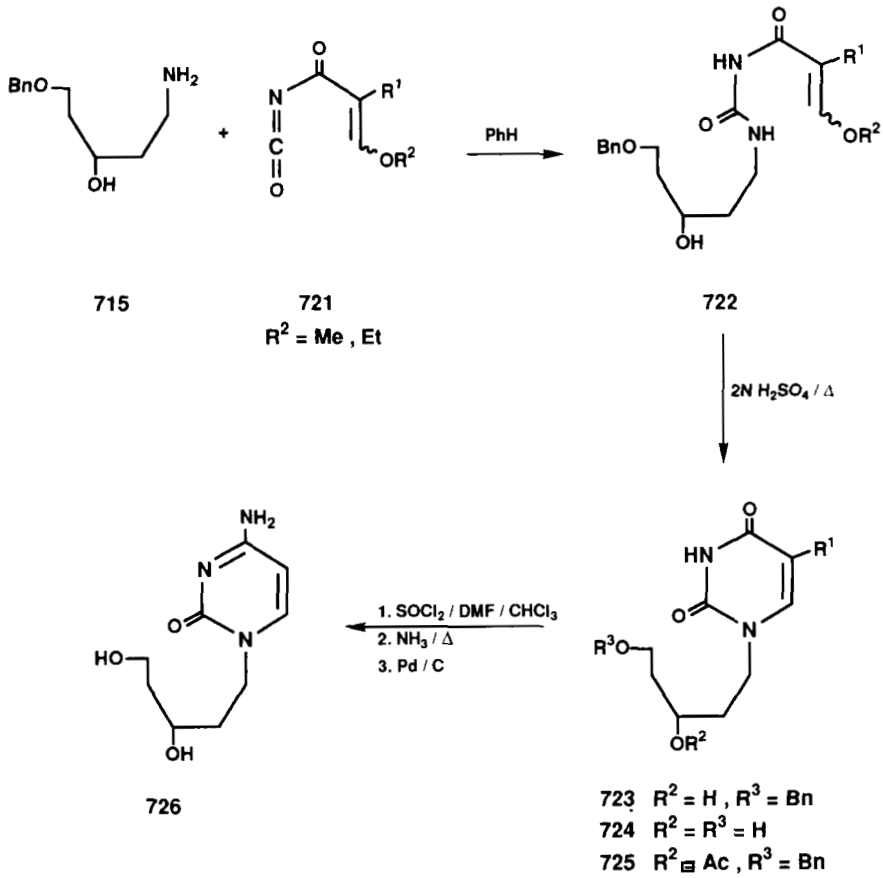
The cytosine analog **726** was synthesized by reacting **715** with isocyanate **721** to give **722.** Cyclization then gave **723,** which was deprotected to form



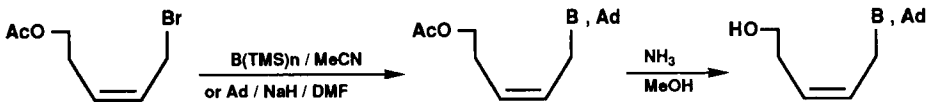
SCHEME 139

724. The cytidine analog was prepared from **725** by chlorination, aminolysis, and deprotection to give **726** (90JMC2476). The compound displayed no anti-HIV activity, indicating that replacement of the carbohydrate moiety of the different naturally occurring nucleosides by a pentane-3,5-diol chain does not give rise to antiviral activity against HSV-1, HCMV, and HIV-1.

Acyclic nucleoside analogs were prepared containing C-5′ hydroxyalkyl fragments, where the distance between the 5′-hydroxyl group and the heterocyclic moiety corresponds to that in dideoxydidehydronucleosides (as confirmed by computer modeling). Condensation between 5-*O*-acetyl-1-bromo-2-pentene (**727**) and persilylated heterocyclic bases (pyrimidines and guanine) or adenine sodium salt gave rise to the acyclic nucleosides **728.** Deprotection by NH_3/MeOH gave the desired nucleosides **729** (91MI1).



SCHEME 140



727
B = Th , Cy , Gu

728

729

SCHEME 141

G. 1′,*x*- AND 4′,5′-*diseco*-NUCLEOSIDES (TYPE 2.7)

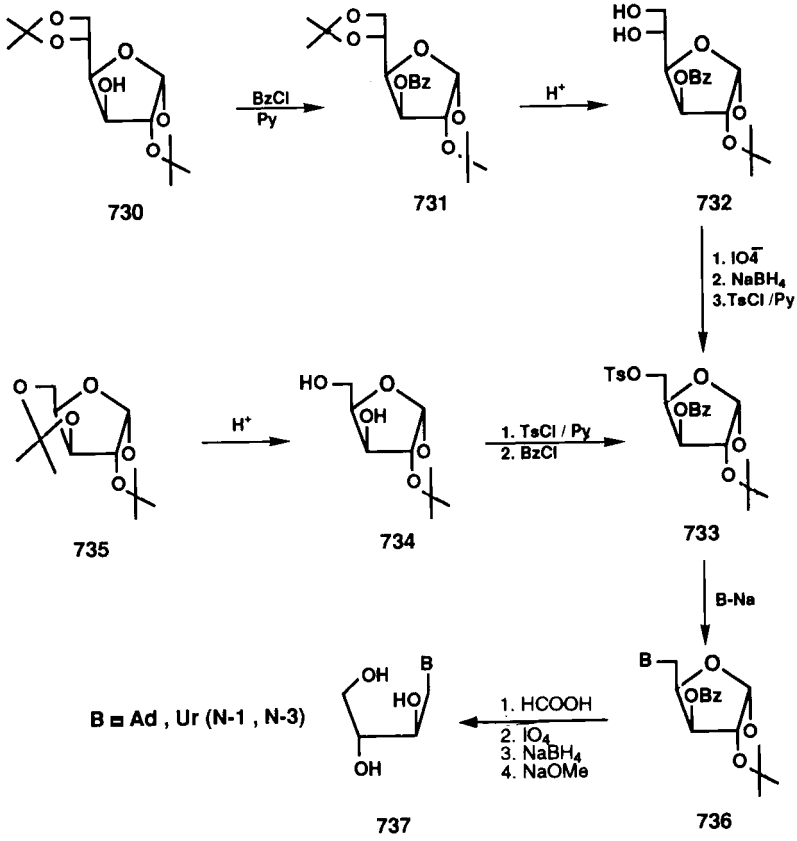
1. *Acyclo-N-Nucleoside Analogs*

The starting **733** could be prepared from the D-glucose derivative **730** by benzoylation to **731,** followed by partial deisopropylidenation to **732** and then periodate oxidation, reduction, and tosylation. Alternatively, it was formed from the D-xylose derivative **735** by partial hydrolysis to **734,** followed by tosylation and then benzoylation. Reaction of **733** with the sodium salt of bases gave **736.** Hydrolysis of the isopropylidene group followed by periodate oxidation, reduction, and then debenzoylation gave **737** (79CCC593).

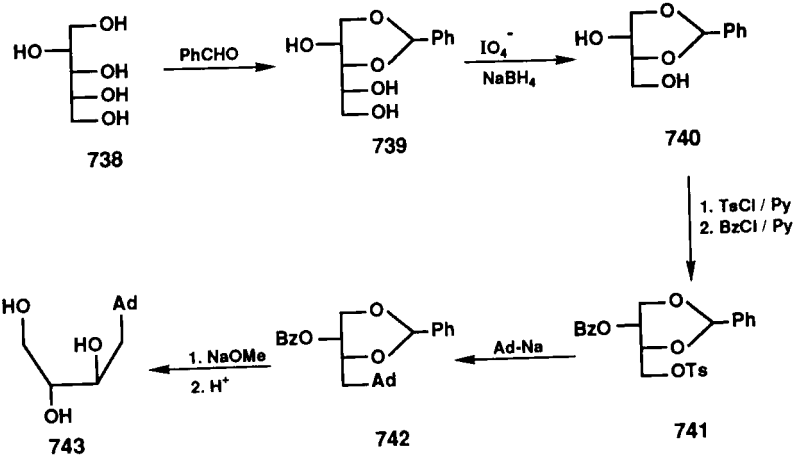
The synthesis of the enantiomeric *threo* analogs started from D- or L-arabinose (79CCC593). Thus, the adenine analog **743** was prepared from D-arabinitol **738** by conversion to the benzylidene derivative **739.** Its periodate oxidation and reduction gave **740,** which was tosylated and then benzoylated to give **741**. Reaction of **741** with the sodium salt of adenine gave **742,** which was deprotected to give **743.**

The racemic DL-threo derivative **747** was prepared starting from ethyl DL-tartarate, whose reaction with dimethoxypropane gave **744.** Subsequent reactions, as shown in Scheme 144, gave **745,** then **746,** which was deprotected to **747.** An analogous synthetic procedure was also done for the preparation of the racemic erythro derivative (79CCC593).

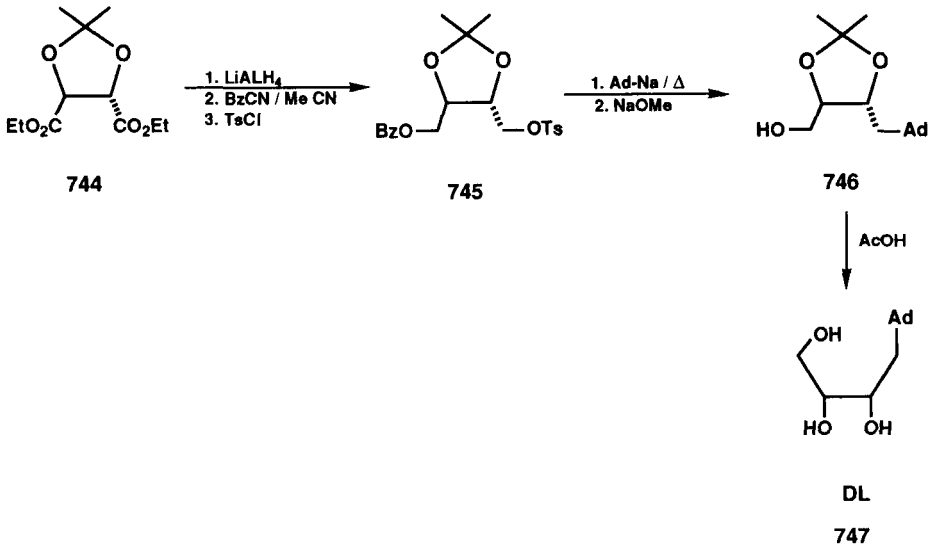
Eritadenine (**750**) is one of the significant hypo-cholesterolemic components of *Lentinus edodes sing.* Moreover, eritadenine and its stereomers have antiviral effects against vaccinia, vesicular stomatatis virus, and measles (85MI4). Several methods has already been elaborated for its synthesis. Thus, reaction of 4-amino-4-deoxy-D-erythronic acid (**748**) with 4-amino-6-chloro-5-nitropyrimidine followed by reduction of the nitro group gave **749,** whose cyclization with formamide gave **750** (69E1237). The condensation of 2(*R*),3(*R*)-*O*-protected dihydroxybutyrolactone **754** with the sodium



SCHEME 142

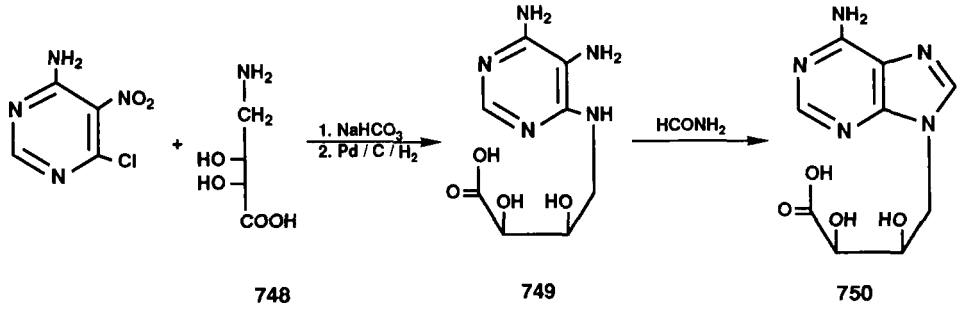


SCHEME 143

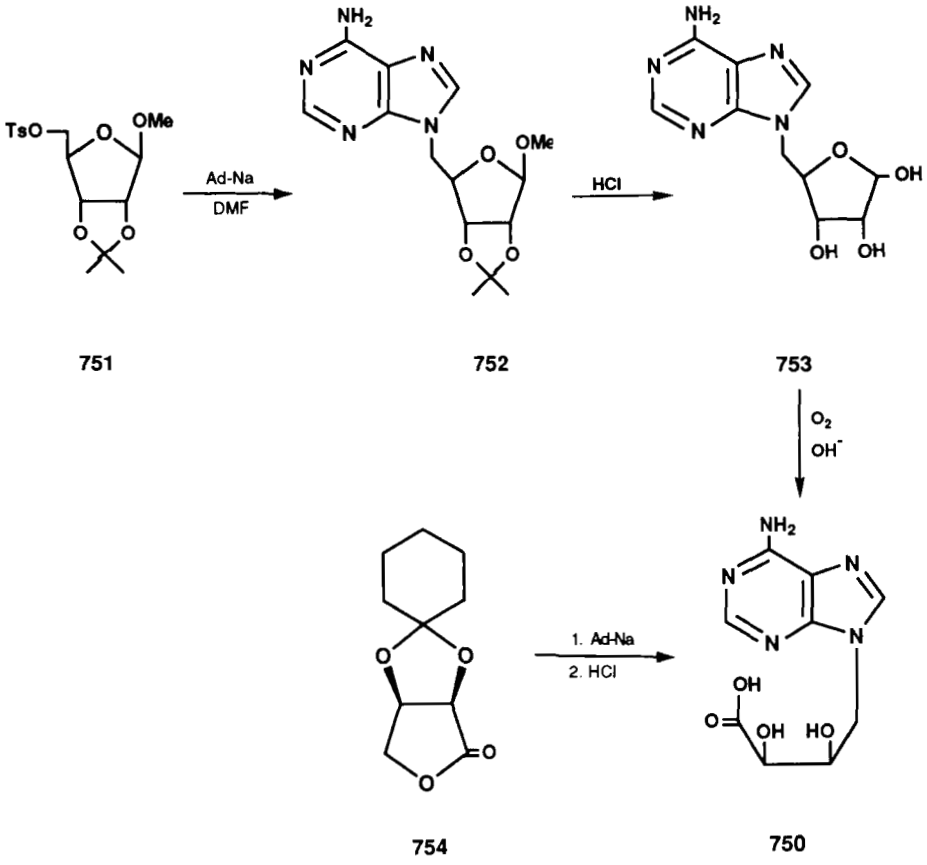


SCHEME 144

salt of adenine followed by hydrolysis gave **750** (71JOC1573). Alternatively, reaction of methyl-5-*O*-tosyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (**751**) with the sodium salt of adenine gave the corresponding reversed nucleoside **752,** whose deprotection gave **753** and whose oxidation gave **750** (73JOC2887). This approach is convenient and was used successfully for the synthesis of analogs with different configurations and chain lengths [70JCS(CC)1047]. The enantiomeric and racemic forms were also prepared (84MIP1). The ethyl-4-(2-amino-6-chloropurin-9-yl)-2-hydoxybutyrate was prepared by alkylation with the 2-hydroxy-4-bromobutyrate ester (85USP4495190).

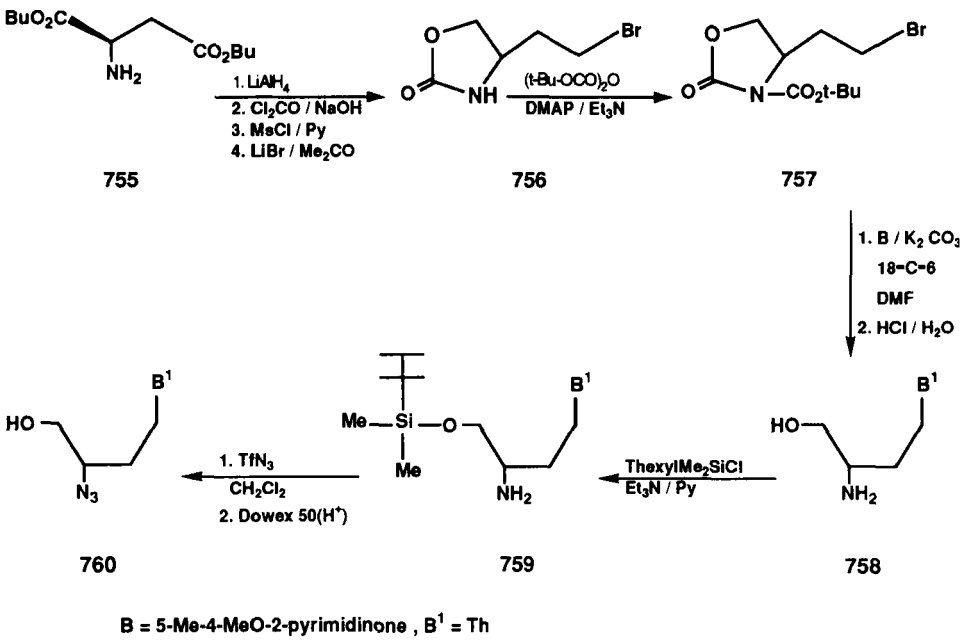


SCHEME 145



SCHEME 146

A modified analog of this type (**760**) was prepared from the di-*n*-butyl ester **755** of *R*(−)-aspartic acid, which was reduced to the diol and then to the oxazolidinone by reaction with phosgene, followed by mesylation and displacement of the mesylate group by bromide ion to give **756,** which subsequently was converted to the N-BOC **757.** Regioselective formation of the desired N-1 alkylated thymine derivative was achieved in three operations involving reaction of **757** with 4-methoxy-5-methyl-2-pyrimidinone in DMF/K_2CO_3, followed by opening of the oxazolidinone ring, N-BOC deprotection, and concomitant liberation of the C-4 amide carbonyl. Derivatives of the amino group of **758** were prepared by reaction of **758** with KOCN/H_2O, with $H_2CO-HCO_2H$ or CNBr. The 3′-azido analogs **760** were prepared by reacting the *O*-protected amine **759** with

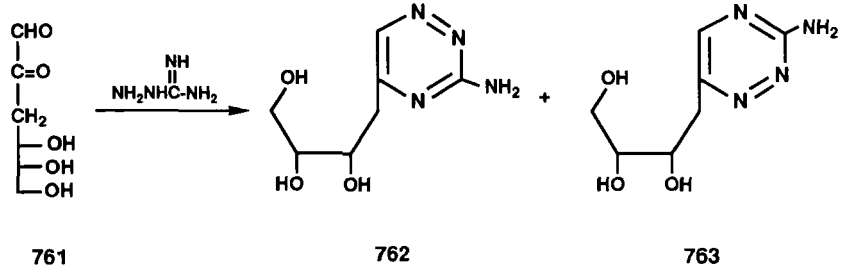


SCHEME 147

freshly prepared triflyl azide, followed by liberation of the 4′-hydroxyl group using DOWEX (90TL4879).

2. *Acyclo-C-Nucleoside Analogs*

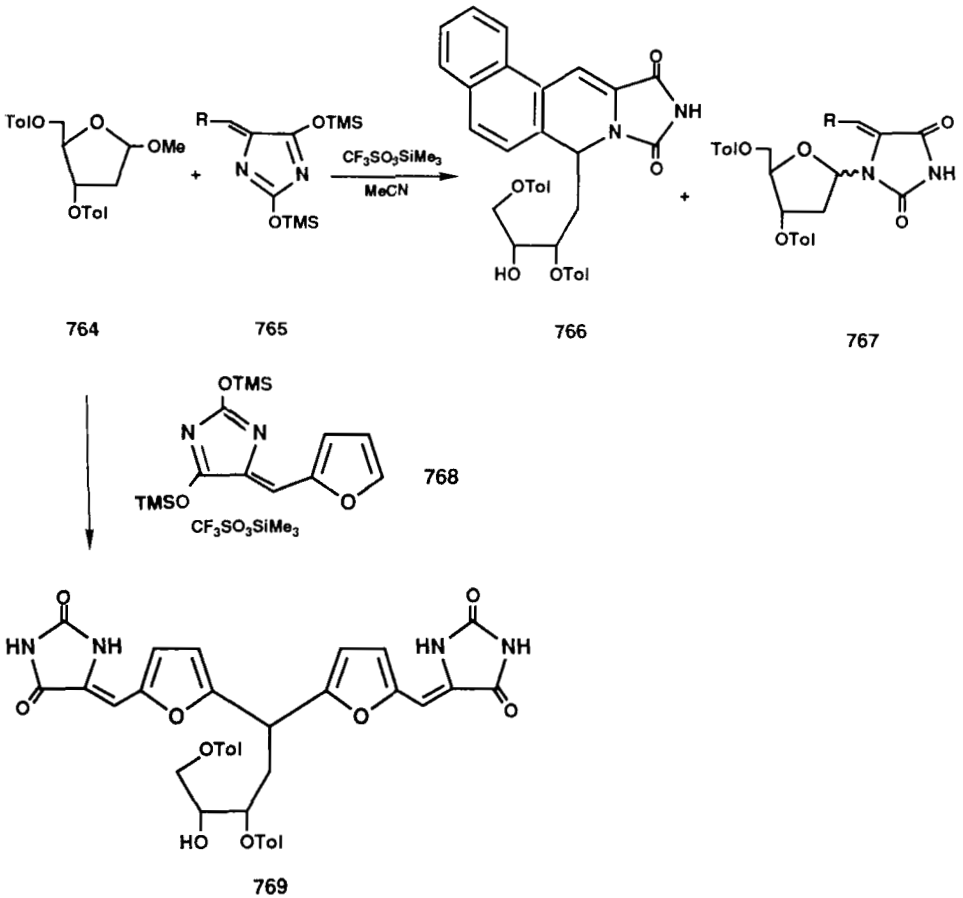
Reaction of 3-deoxyglucosulose **761** under physiological conditions with aminoguanidine gave a mixture of the two isomeric triazines **762** and **763** (92MI4).



SCHEME 148

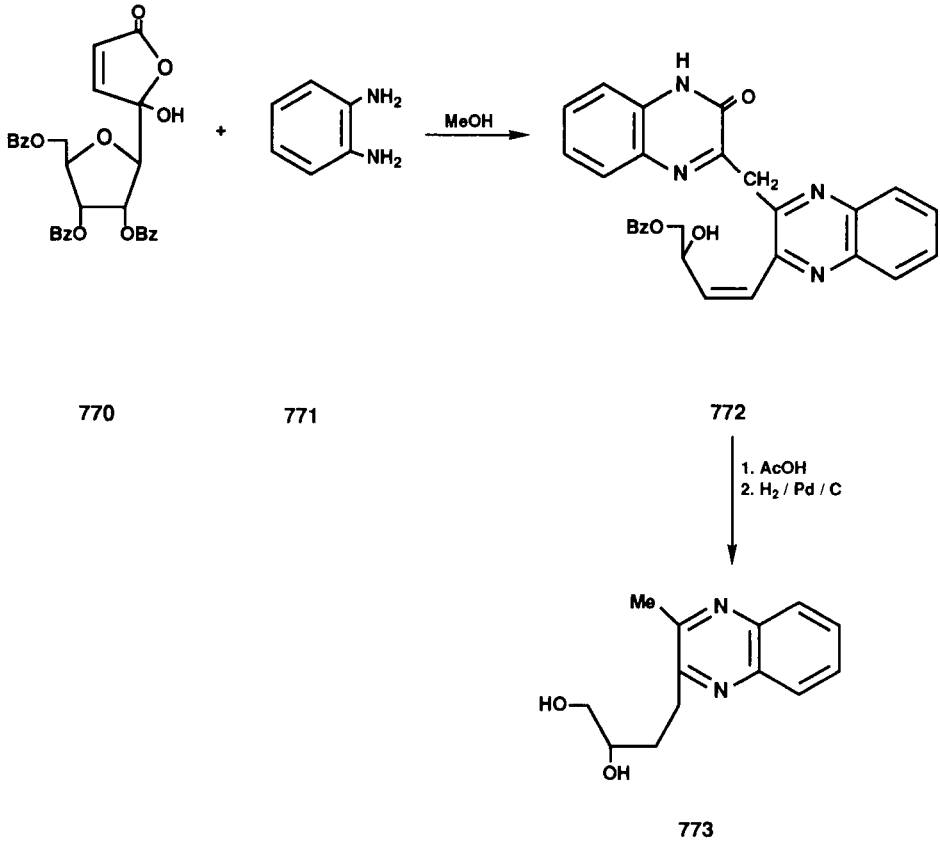
Reaction of methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranoside **764** with the trimethylsilyl derivatives of hydantoin **765** and **768** in presence of TMS triflate gave **766** and **769,** respectively (93JOC5994). The anticipated nucleoside **767** was formed in low yield in the former reaction. The formation of the acyclic analogs was accounted for by assuming the initial step to be a ring opening of the sugar to give an acyclic glycos-1-yl cation.

Treatment of 1,2-diaminobenzene **771** with the furanone glycoside **770** in methanol gave the olefin **772.** Treatment of **772** with AcOH followed by catalytic hydrogenation produced 2-[4-*O*-benzoyl-(3*S*)-3-hydroxybutyl]-3-methylquinoxaline, whose debenzoylation gave **773** (93H2591).



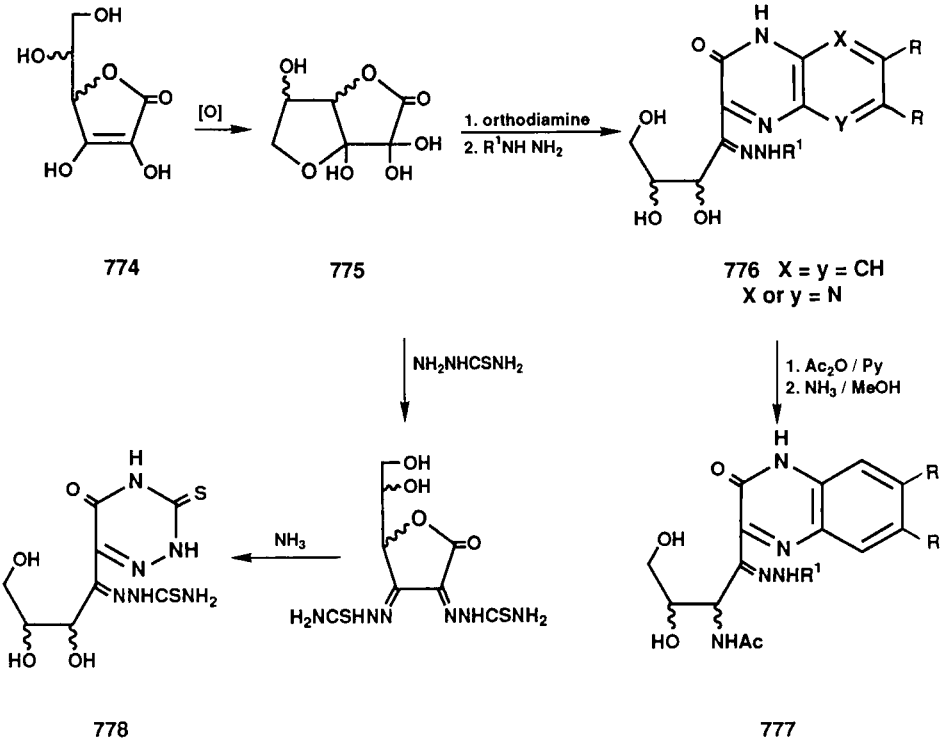
SCHEME 149

Oxidation of L-ascorbic acid and analogs generally formulated as **774** gave the dehydro derivatives **775,** whose reaction with 1,2-diaminobenzene or its derivatives were followed by reaction with different types of hydrazines to afford the quinoxaline derivatives **776** [78MI2, 78MI3, 78MI4, 78MI5; 82MI1; 86MI1; 88MI3; 90JCS(P1)2513]. The use of 2,3-diaminopyridine gave the two corresponding isomeric products (96UP3). However, reaction of **775** with thiosemicarbazide gave the respective bis(thiosemicarbazone); ring opening of the lactone followed by cyclization of the C-2 thiosemicarbazone residue with the C-1 generated carboxylic group gave **778** (92AHC233). Acetylation of **776** followed by deacetylation with methanolic ammonia gave **777** (92MI2).



770 771 772 773

SCHEME 150



SCHEME 151

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