Chapter 4
Nucleoside Mimetics

Modified nucleosides are useful therapeutic agents being currently used as antitumor, antiviral, and antibiotic agents. Despite the fact that a significant variety of modified nucleosides display potent and selective action against cancer, viral and microbial diseases, the challenge still attracts full attention since most of them do not discriminate between normal and tumor cell and in viral infections resistant strains usually appear during the course of the treatment.

Synthetic acyclic and carbocyclic *C*-nucleosides and modified *N*-nucleosides have shown remarkable action against AIDS, Hepatitis, and herpes infections among others. Some of the nucleosides used as approved drugs are: acyclovir, carbovir being the treatment of choice against herpes, AZT, ddI, ddC, ddG, abacavir, which in combination with protease inhibitors are indicated in the treatment against HIV, and *C*-nucleoside ribavirin in the treatment against hepatitis [1, 2].

Representative examples of chemotherapeutic agents modified at the heterocyclic base, the sugar fragment, L and *C*-nucleosides, carbocyclic and acyclic nucleosides are depicted in Scheme 4.1.

A significant number of synthetically modified nucleosides have been designed as antiretroviral drugs in the therapy of human immunodeficiency virus (HIV) infection. During retroviral infection, the viral RNA is used as template for proviral DNA synthesis, a process mediated by viral DNA polymerase better known as reverse transcriptase. Thus, the process involves the initial formation of a RNA–DNA hybrid which is then degraded by an RNAse to release the DNA strand that will be the template for the synthesis of the double stranded viral DNA, a process also catalyzed by reverse transcriptase [3].

The proposed mechanism of action of modified agents such as AZT during viral infection involves the interruption of the viral replication process that occurs between the virus and host, particularly the replication inhibition inside T cells, monocytes, and macrophages.

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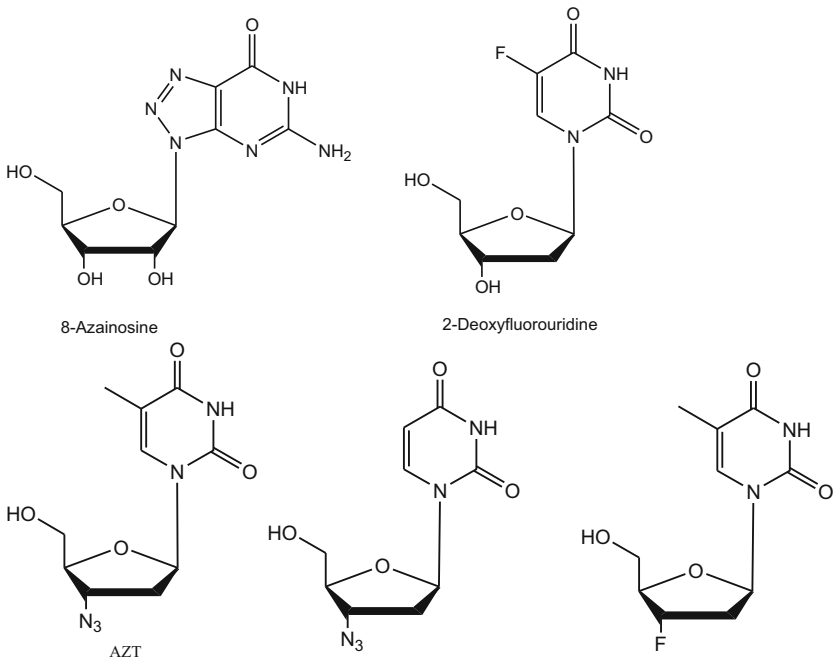


Scheme 4.1 Representative synthetically modified nucleosides

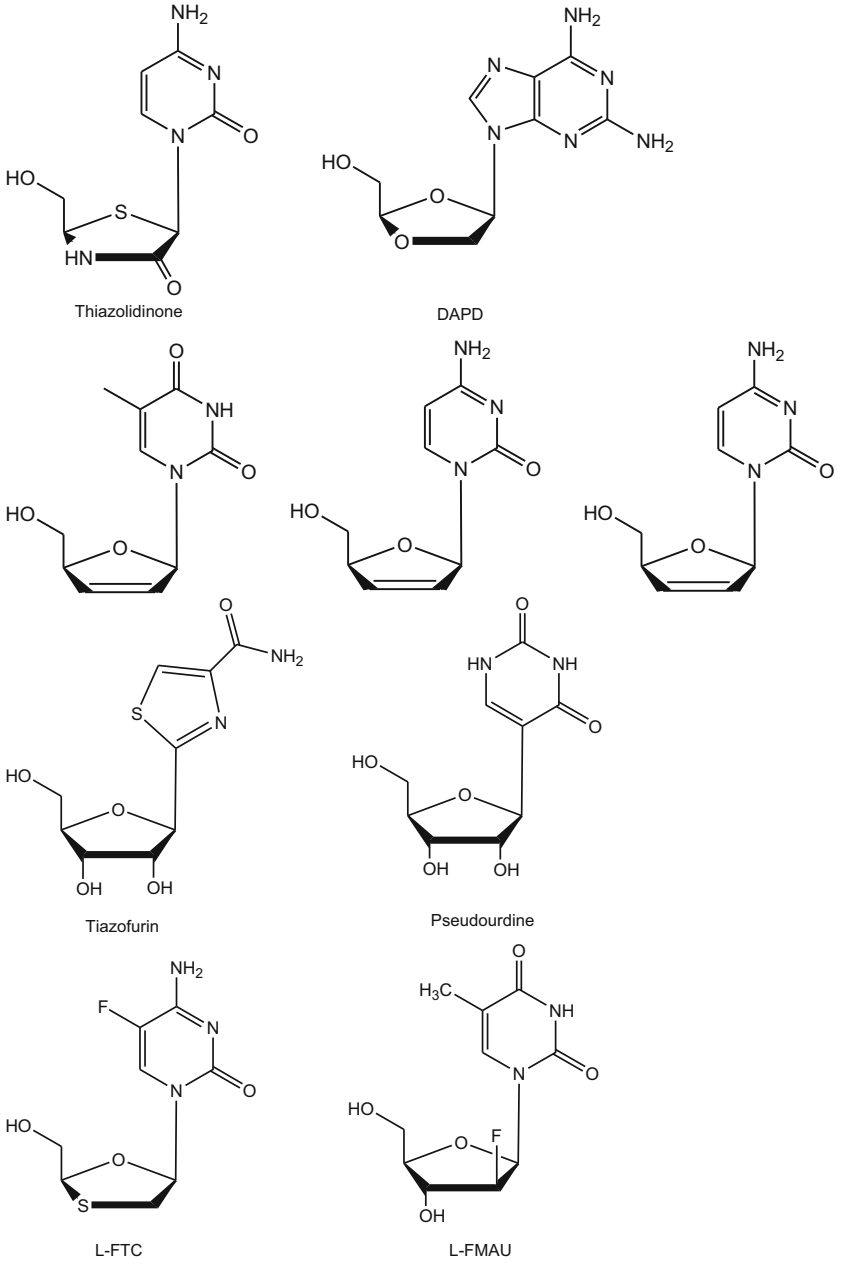
When the modified nucleoside is introduced into the cell, a sequential 5′-phosphorylation process mediated by kinases occurs on the furanoside ring which is subsequently incorporated into the DNA as triphosphate (Scheme 4.2).

An important collection of active nucleosides mimetics has been synthesized and classified for better understanding as follows: [4]

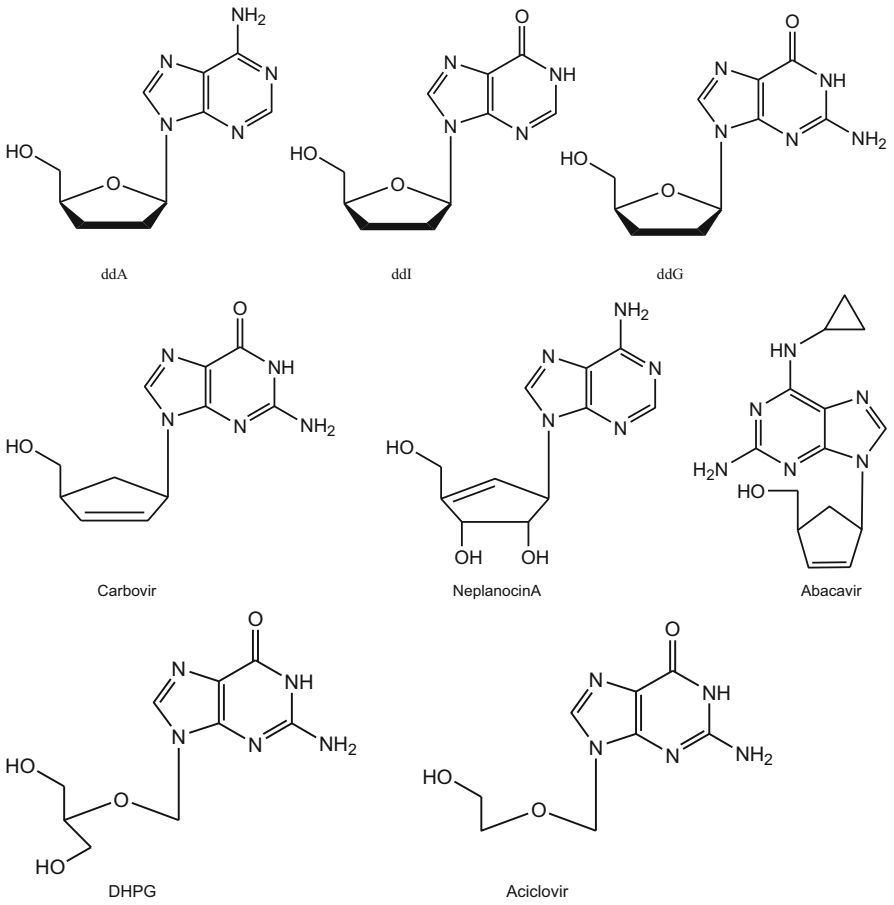
Modified *N*-nucleosides
L-nucleosides (D-isomers)
C-nucleosides
Carbocyclic nucleosides
Acyclic nucleosides
Thionucleosides

4.1 Modified *N*-nucleosides

A broad number of modified *N*-nucleosides have been developed and tested on clinical trials, some of them being highly promising. The chemical manipulations have been made at the heterocyclic base, the sugar of both. Some representative examples of chemical modifications leading to key intermediates or active nucleosides are:



Scheme 4.1 (continued)



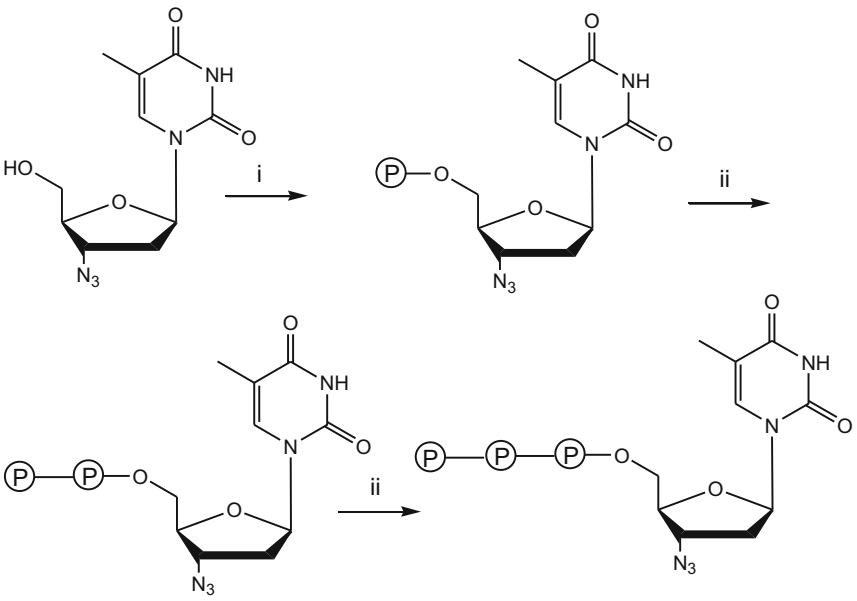
Scheme 4.1 (continued)

4.1.1 Heterocycle Modifications

4.1.1.1 C-5 Substituted Pyrimidines

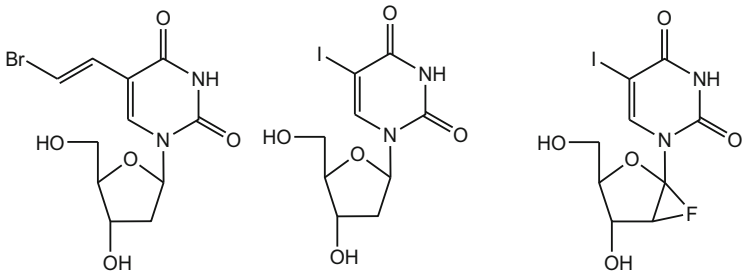
Several nucleoside analogs bearing modifications at the 5-position have been found to be active as antiviral and anticancer drugs. Examples of this are BVDU, IDU, and FIAU (Scheme 4.3) [5].

Palladium mediated transformations are a suitable strategy for introducing substituents at C-5. Some of the reactions implemented for this purpose are the Sonogashira [6, 7], Stille [8, 9], Heck [10, 136], and Hiyama [11] (Scheme 4.4).



i) Timidinkinase. ii) Timidilatokinase. iii) Nucleosidediphosphatekinase.

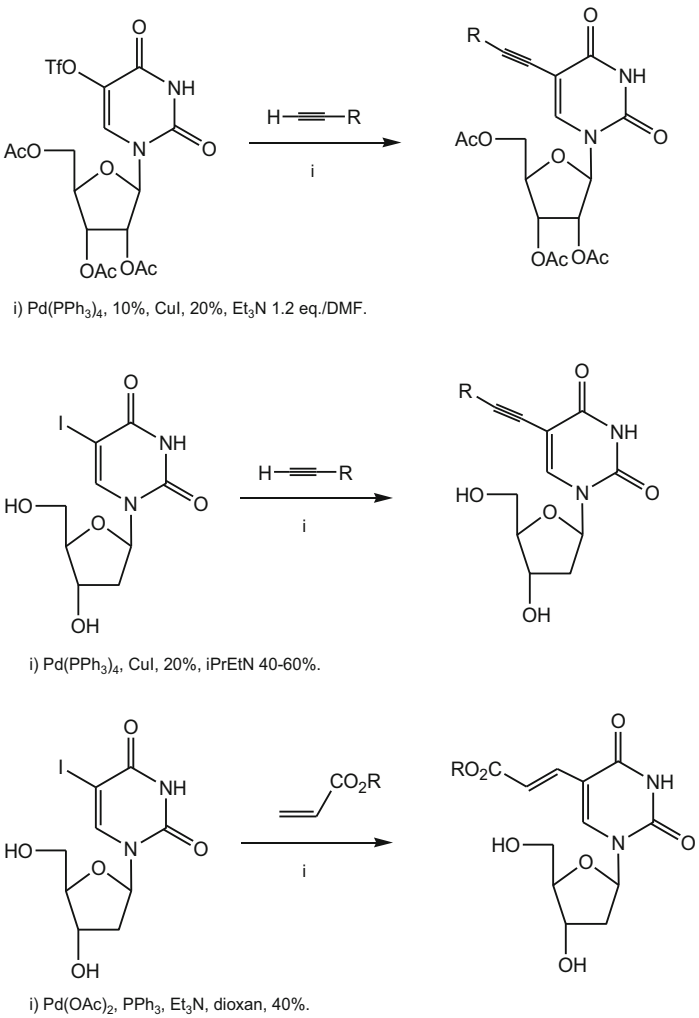
Scheme 4.2 Phosphorylation of AZT



Scheme 4.3 Active C-5 substituted pyrimidines

4.1.1.2 C-6 Substituted Pyrimidines

By following palladium-mediated substitutions, a more limited number of C-6 substituted pyrimidines have been described in comparison with C-5. For instance, by applying the Stille reaction it has been possible to prepare C-6 substituted aryl, vinyl, alkynyl derivatives (Scheme 4.5) [12].

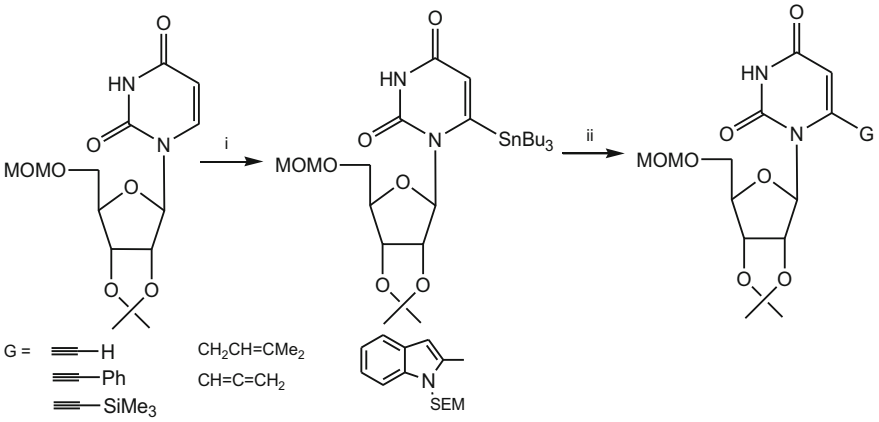


Scheme 4.4 Palladium mediated substitutions at C-5 pyrimidine position

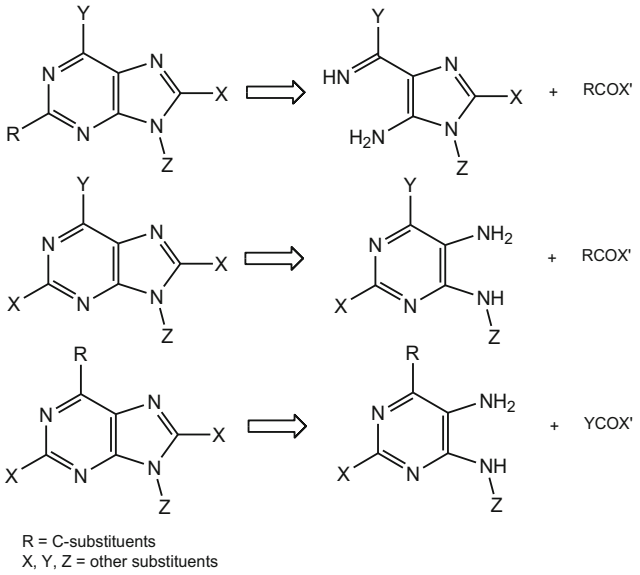
4.1.1.3 Purine Formation

The conventional methods of preparation of C-C purines are based on heterocyclization [13, 14]. The classical procedures involve:

(a) 2-C-C-purines cyclization of 4-aminoimidazole-5-carboxamides or nitriles with carboxylic acid equivalents.
(b) 8-C-C-purines from 5,6-diaminopyrimidines and carboxylic acid derivatives; and for 6-C-C-purines from 4-alkyl or 4-aryl-substituted 5,6-diaminopyrimidines (Scheme 4.6) [15].

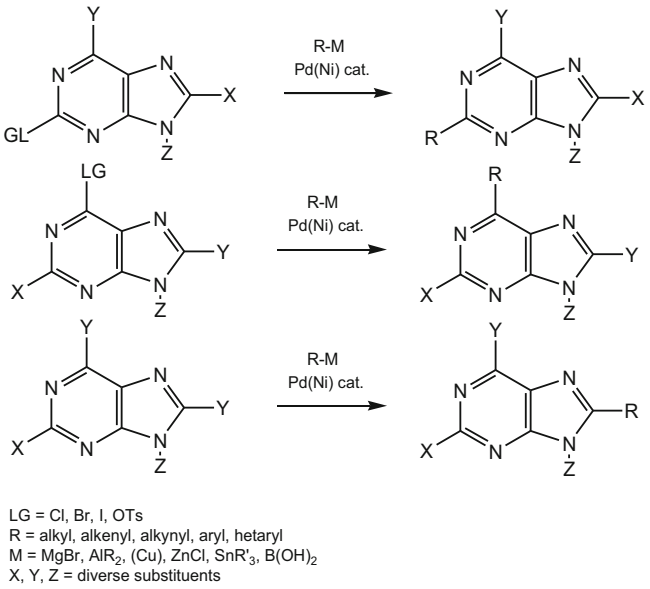


Scheme 4.5 Palladium-mediated substitution of 6-C substituted pyrimidines



Scheme 4.6 Conventional methods of preparation of C-C purines

Other explored methods involve radical [16, 17] or nucleophilic substitution [18], sulfur extrusion [19], and Wittig type reactions [20, 21]. Despite their usefulness, other methods based on the use of organometallic complex are getting particular significance especially in the synthesis of substituted purines (Scheme 4.7) [15].



Scheme 4.7 General scheme between purines and organometallic compounds

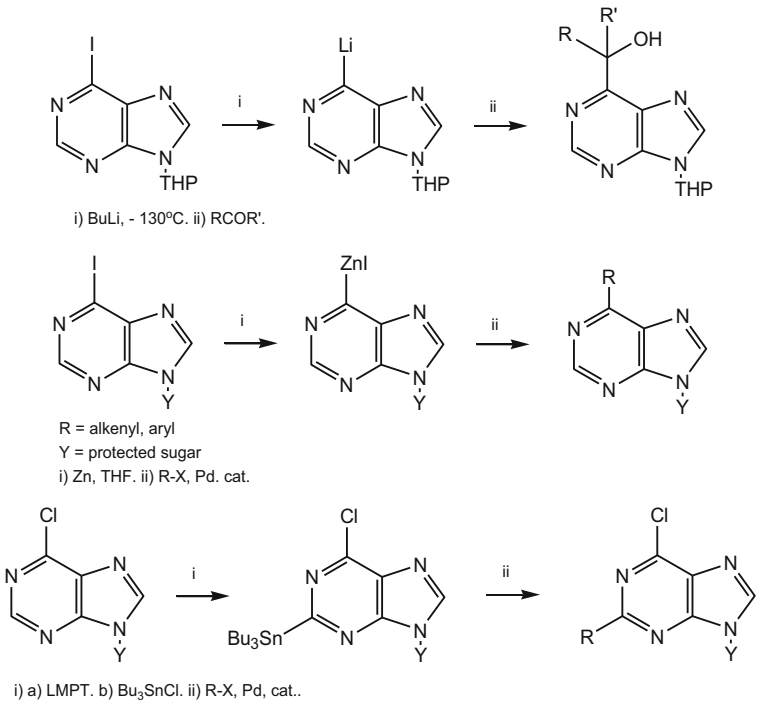
Usually the cross-coupling reactions involving organometallic compounds includes organolithium [22], magnesium [23], aluminum [24], cuprates [25], zinc [26], stannanes [27], and boron [28] reagents, in the presence of palladium catalyst and the purine base bearing a good leaving group usually halides or tosyl (Scheme 4.8).

Deazapurines are pyrrolo[2,3]pyrimidines of natural or synthetic source with significant antitumor, antiviral and antibacterial activities. Some compounds included in this class are tubercidin, toyocamycin, sangivamycin, and the hypermodified nucleoside queuosine. A flexible route for the preparation of pyrrolo[2,3] pyrimidines (7-deazapurines) has been developed, consisting in the condensation of protected uracil with ethyl *N*-(*p*-nitrophenethyl)glycinate and subsequent treatment with acetic anhydride and amine base with heating to provide 5-(acetyloxy) pyrrolo[2,3-d]-pyrimidine-2,4-dione in 74 % yield (Scheme 4.9) [29].

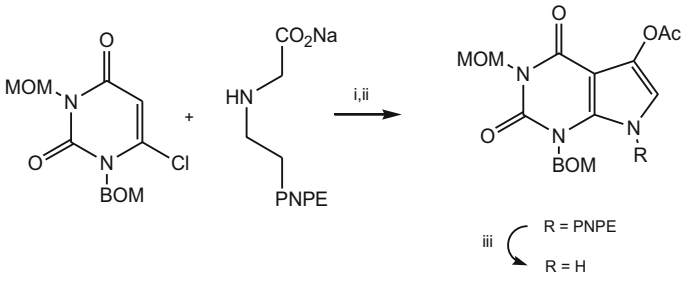
4.1.2 Sugar Modifications

4.1.2.1 2′-3′-dideoxysugars

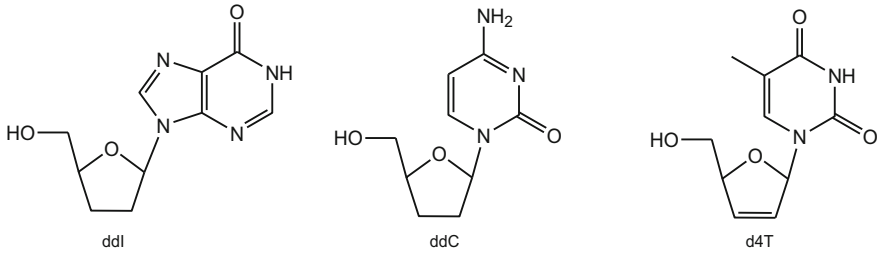
A significant number of saturated and unsaturated dideoxysugars have been synthesized and tested as antiviral or anticancer drugs. Remarkably, ddI and ddC are approved drugs for the treatment of AIDS [3], and others such as d4T being currently under clinical studies (Scheme 4.10) [30, 31].



Scheme 4.8 Cross-coupling reactions for purine modification



Scheme 4.9 Synthesis of 7-deazapurine analogs

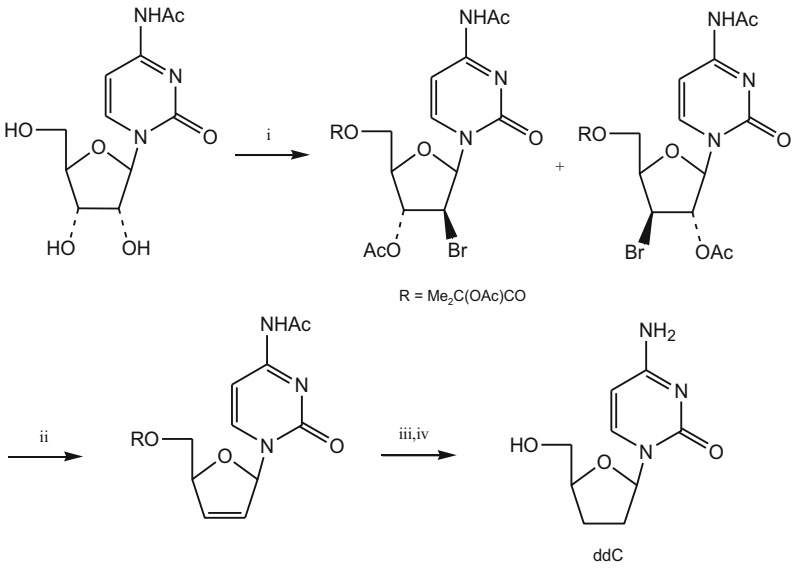


Scheme 4.10 Anti-AIDS 2′3′-dideoxy nucleosides

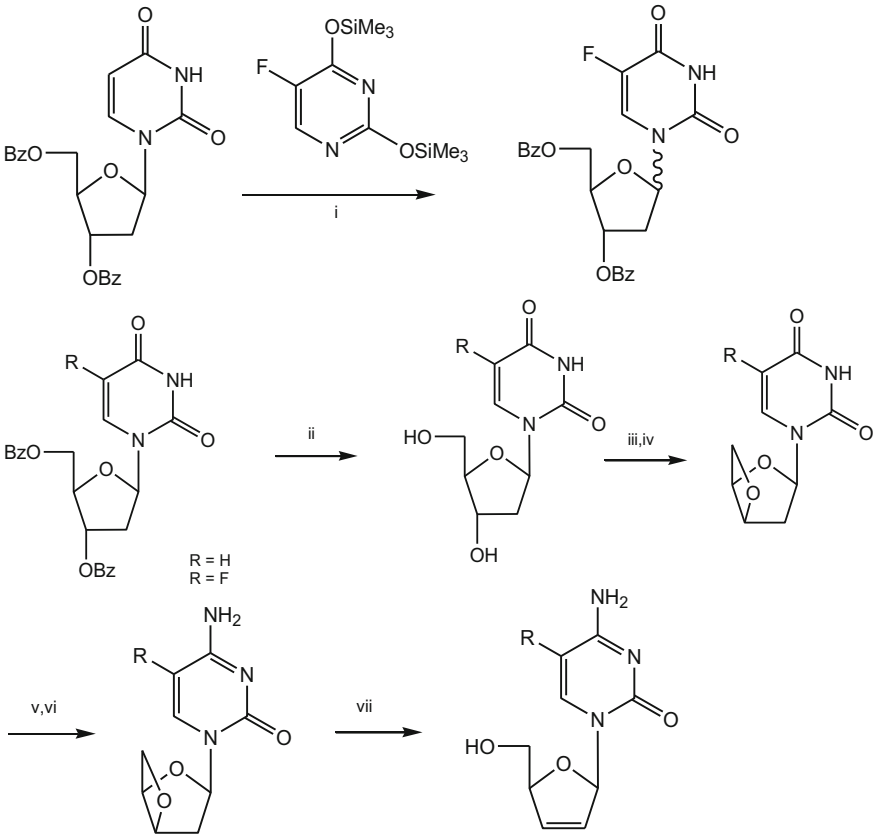
A method for preparing ddC was described involving bromoacetylation with HBr in acetic acid of N^4-acetylcytidine followed by reductive elimination with zinc–cooper couple in acetic acid to provide the corresponding 2′3′-unsaturated derivative. Final hydrogenation over 10 % palladium on charcoal gave ddC in 95 %. accompanied by some N-C cleavage in 5 % (Scheme 4.11) [32]. Similar reaction conditions were used for preparing 2′3′-dideoxyadenosine in 81 % yield from adenosine [33].

The design and synthesis of potent inhibitors for human hepatitis B Virus (HBV) 2′,3′-dideoxy-2′3′-didehydro-β-L-cytidine (β-L-d4C) and 2′,3′-dideoxy-2′3′-didehydro-β-L-5-fluorocytidine (β-L-Fd4C) nucleosides was carried out according to the pathway shown in Scheme 4.12 [34]. The key starting material 3′,5′-dibenzoyl-2′-deoxy-β-L-uridine was submitted to transglycosilation reaction with silylated 5-fluorouracil using TMSOTf as catalyst, providing an anomeric mixture separated by chromatography. After benzoyl deprotection, the anomeric nucleosides were treated with mesyl chloride followed by base to form cyclic ethers. Further transformation at the pyrimidine ring was followed by potassium *tert*-butoxide treatment to furnish β-L-d4C and β-L-Fd4C.

Other methods designed for the preparation of 2′3′-unsaturated and saturated deoxyfuranosides are based on: (a) Corey–Winter reaction involving cyclic thionocarbonate; [35–37], (b) Eastwood olefination process in which a five-membered cyclic orthoformate suffer a fragmentation to give in the presence of acetic anhydride the desired olefin (successfully applied in the preparation of ddU) [38, 39],



Scheme 4.11 Synthesis of anti-AIDS ddC



i) $CF_3SO_3SiMe_3$, CH_3CN. ii) NH_3/MeOH. iii) MsCl, Py. iv) 1N NaOH, EtOH/H_2O. v) 1,2,4-triazole, p-$ClC_6H_4OPOCl_2$, Py. vi) NH_4OH, dioxane. vii) *t*-BuOK, DMSO.

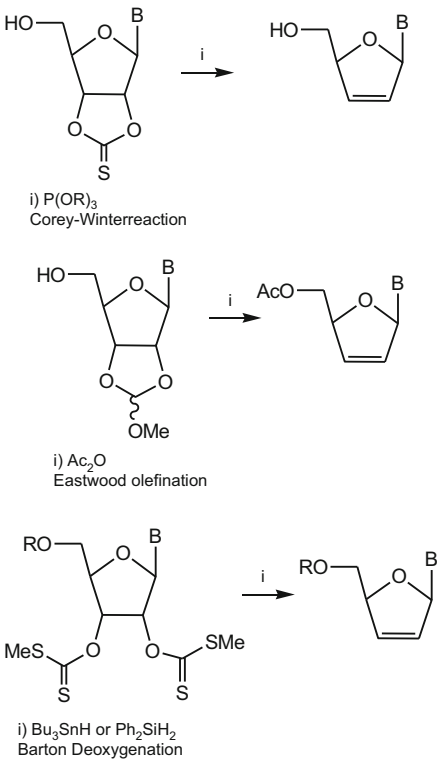
Scheme 4.12 Synthesis of anti-hepatitis B virus β-L-d4C and β-L-Fd4C

and (c) Barton deoxygenation involving the cyclic thionocarbonate or the bisxanthate, and then treated with tributyltin hydride [40, 41], or alternatively diphenylsilane [42] (Scheme 4.13).

The synthesis of modified nucleosides from natural nucleosides is another useful alternative for preparing pharmaceutically active dideoxy nucleosides. The potent antiviral inhibitors ddC, ddG, d4C, and d4G have been obtained from the corresponding protected natural nucleosides, as shown in Scheme 4.14 [43].

The chemoenzymatic approach has been also explored for the synthesis of 2′,3′ dideoxynucleosides. Such is the case of the antiviral 2′,3′-dideoxyguanosine which was synthesized from guanosine in 40 % overall yield using as a key step the commercially available mammalian adenosine deaminase (ADA) (Scheme 4.15) [44].

An strategy for preparing D- and L-2′-fluoro-2′3′-unsaturated nucleosides has been described and their anti-HIV activity evaluated. This approach requires 1-acet



Scheme 4.13 Alternative procedures for preparing 2′3′-unsaturated nucleosides

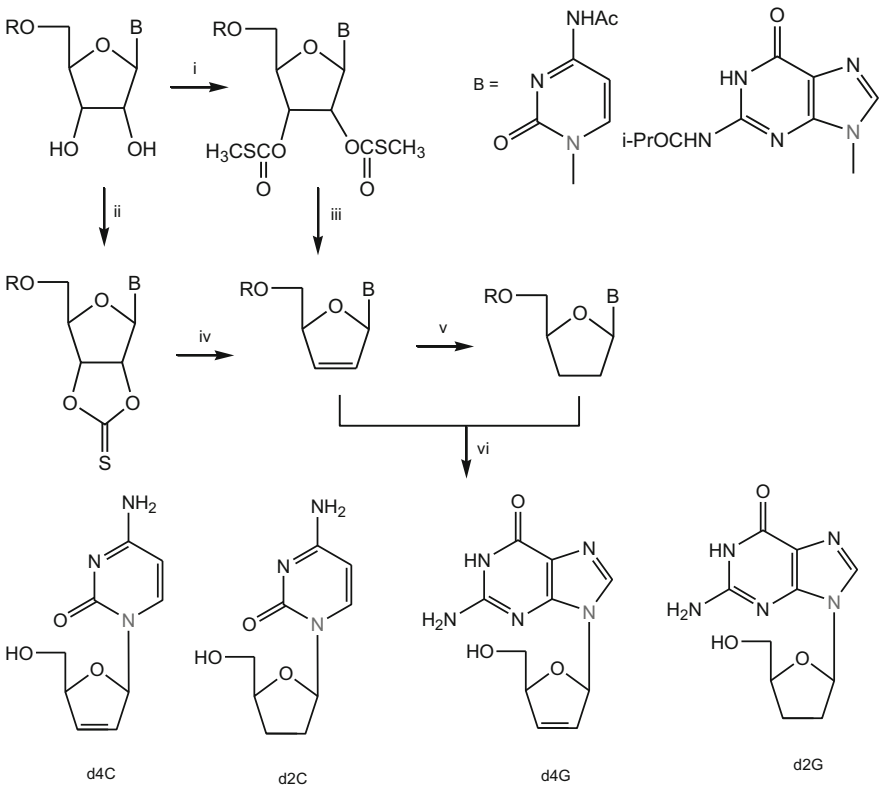
yl-5-*O*-benzoyl-2,3-dideoxy-3,3-difluoro-D-ribofuranose as key starting material which was condensed under Vörbruggen's conditions with purines and pyrimidines to provide the corresponding nucleosides. The resulting nucleosides were subjected to β-elimination to generate the fluoro unsaturated nucleosides (Scheme 4.16) [45].

4.1.2.2 2′-deoxynucleosides

The Barton deoxygenation provides another useful method for preparing 2′- and 3′-deoxynucleosides (obtained as a mixture), and involves as a key step the hydride reduction of the cyclic thionocarbonate with tributyltin hydride [42]. On the other hand, 2′-monotosylate nucleoside when treated with excess of lithium triethylborohydride produces the 2′-deoxy-3′β-hydroxy nucleoside in high yield (Scheme 4.17) [46].

2′-deoxynucleosides have been obtained from starting materials of different composition such as α,β-unsaturated aldehydes [47] chiral epoxy alcohols [48], butenolides [49, 50] and polyfunctionalized acetals among others [51].

The remarkable 2′-deoxynucleoside AZT widely prescribed as anti-AIDS drug was originally prepared from thymidine by Horwitz and coworkers [52], and since



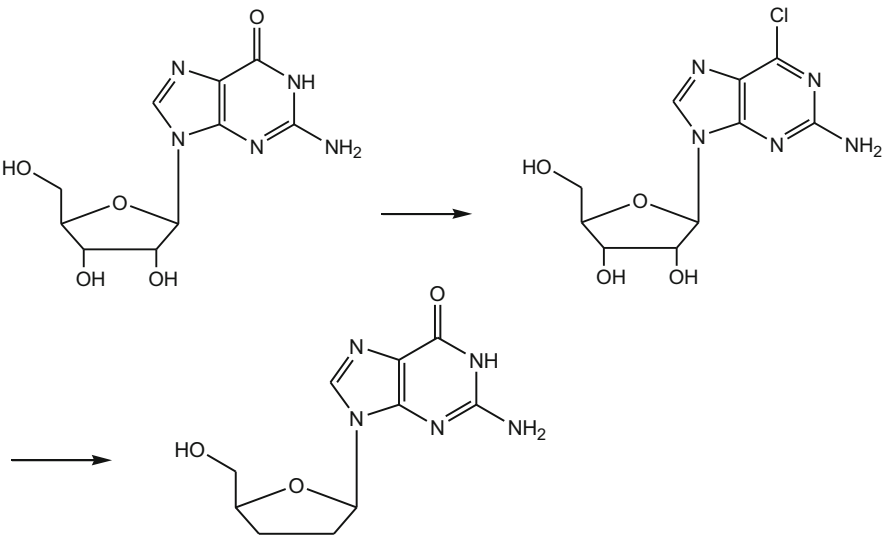
i) NaOH, CS_2/CH_3I. ii) $(Im)_2C{=}S$. iii) Bu_3SnH. iv) $(EtO)_3P$.v) H_2, Pd-C. vi) NH_3/MeOH.

Scheme 4.14 Antiviral modified nucleosides from natural sources

then, several other synthesis have been developed, some of them starting with either a nucleoside, or a sugar derivative [53–56], and others relaying on the use of non-carbohydrate starting materials [56, 57].

The procedure developed by Chu et al. [50] consisted in the use of mannitol as staring material which was subsequently transformed to provide the protected key intermediate 3′-azide-2′-deoxyribofuranose. The next step involved the coupling reaction with silylated thymine under Vörbruggen's conditions to produce an anomeric mixture of nucleosides in 66 %. Final desilylation and separation by chromatography column provided AZT in overall yield of 25 % from the furanoside intermediate (Scheme 4.18).

Another possibility was described by Hager and Liotta involving the coupling reaction between the azido diol intermediate and silylated thymine under Vörbruggen conditions to yield a diastereomeric mixture of azido diol nucleoside. Finally when exposed to concentrated acidic conditions the open form is converted into the β-anomer of AZT in 67 % yield (Scheme 4.19) [57].



i) adnosine deaminase, phosphate buffer, pH 6.5.

Scheme 4.15 Chemoenzymatic synthesis of 2′,3′-dideoxyguanosine

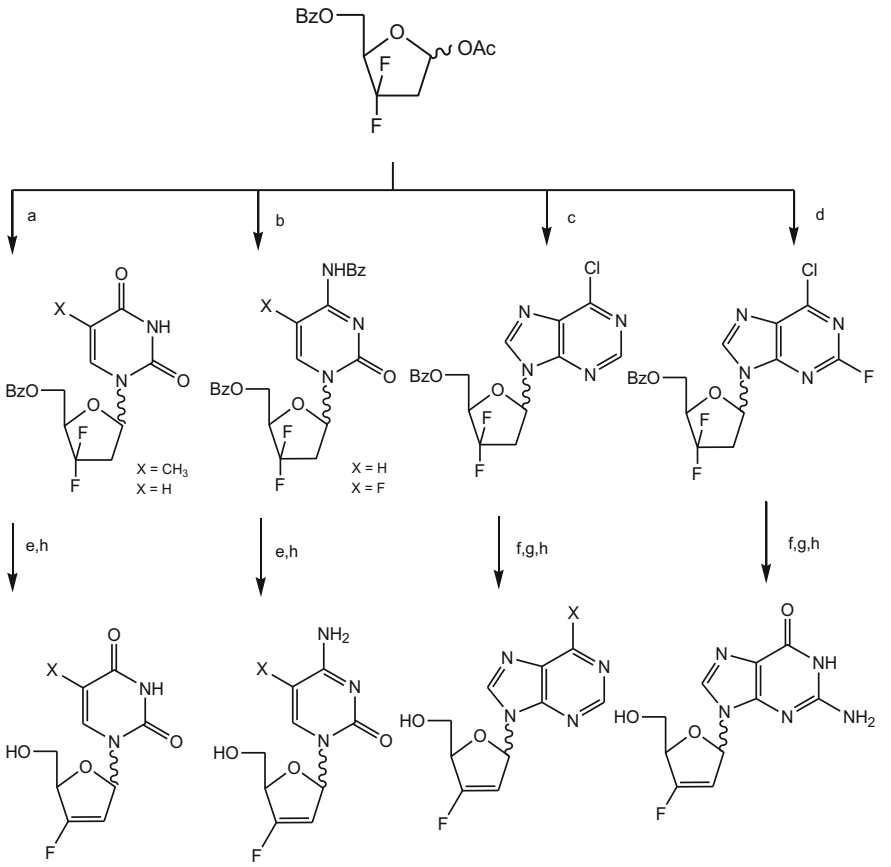
Transglycosidic reaction mediated by a deoxyribosyl transferase obtained from *E. coli* has been used in the synthesis of 3′-azido-2′,3′-dideoxyguanosine. The enzymatic reaction occurs between AZT which acts as glycosyl donor and substituted 2-amino-6-purines to generate the desired purine nucleoside and thymine as by-product (Scheme 4.20) [58].

4.1.2.3 3′-deoxynucleosides

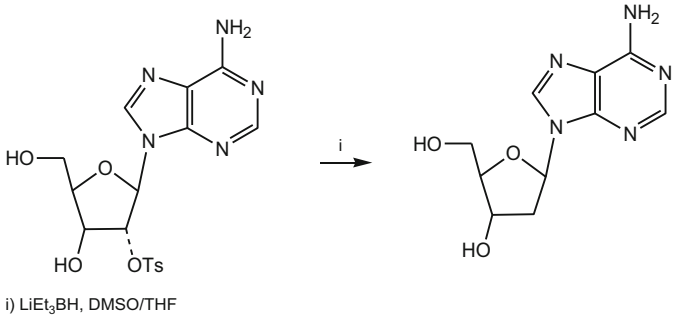
These deoxynucleosides may be readily prepared from 3′-*O*-tosylate via a [1,2]-hydride shift from C3′ to C2′ position with accompanying inversion of the C2′ center providing a 3′-ketone which was stereoselectively reduced by the hydride to produce 3′-deoxynucleoside (Scheme 4.21) [2, 46].

Also 3′-deoxyguanosine was synthesized by an enzymatic transglycosylation of 2,6-diaminopurine using 3′-deoxycytidine as a donor of the sugar moiety. The diaminopurine nucleoside was transformed to 3′-deoxyguanosine by the action of adenosine deaminase (Scheme 4.22) [59].

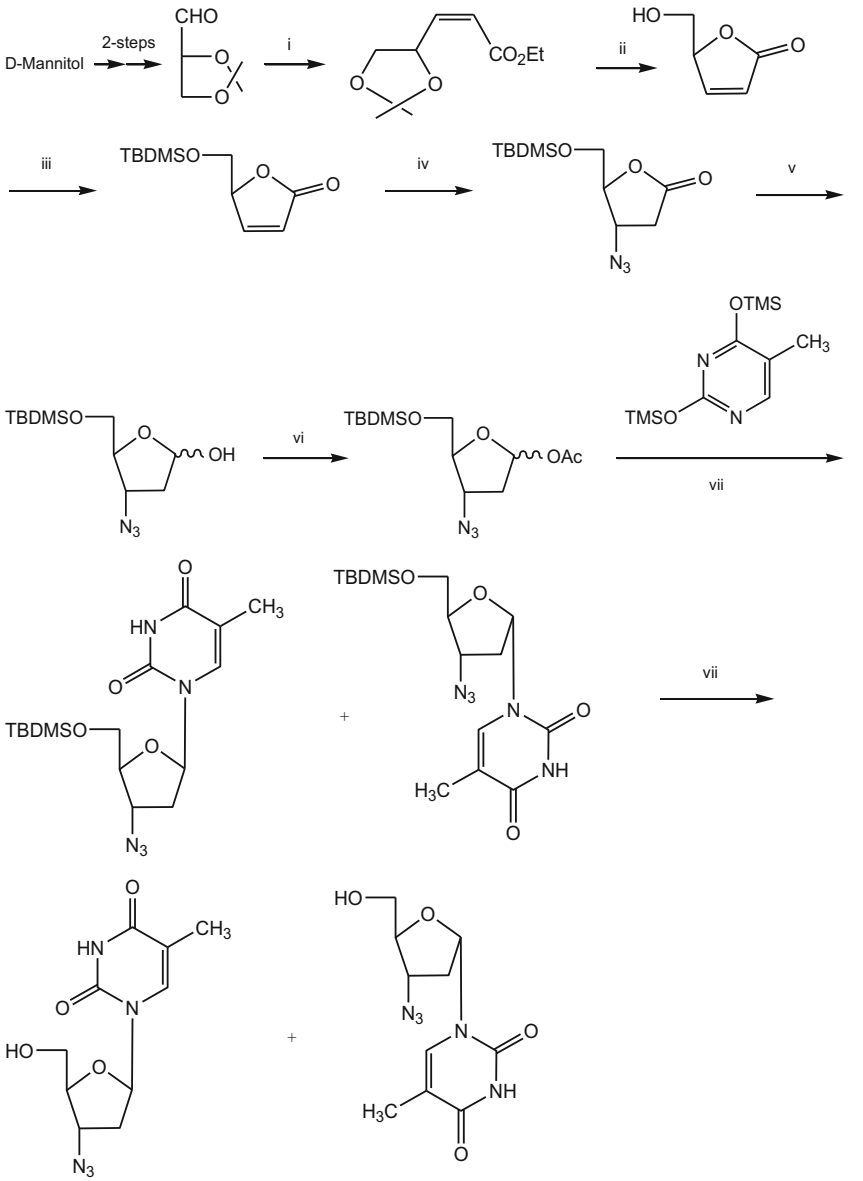
Lodenosine [9-(2,3-dideoxy-2-fluoro-β-D-threo-pentofuranosyl)] adenine (FddA) is a reverse transcriptase inhibitor with activity against HIV. This purine analog was evaluated as one of the most selective inhibitors in a series of 2′3′-dideoxyadenosines, although less active than ddA. An efficient method was developed starting from chloropurine riboside which was tritylated and selectively benzoylated at 3′-position. Before fluorination the 2′-hydroxyl group was converted to imidazolesulfonate or



Scheme 4.16 Preparation of D- and L-2′-fluoro-2′3′-unsaturated nucleosides

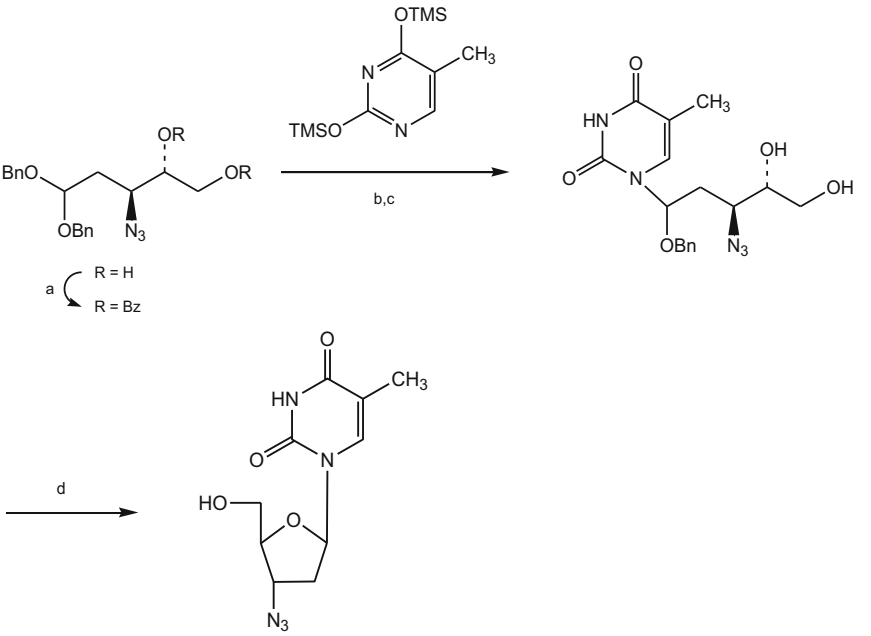


Scheme 4.17 The Barton deoxygenation for preparing 2′-deoxynucleosides



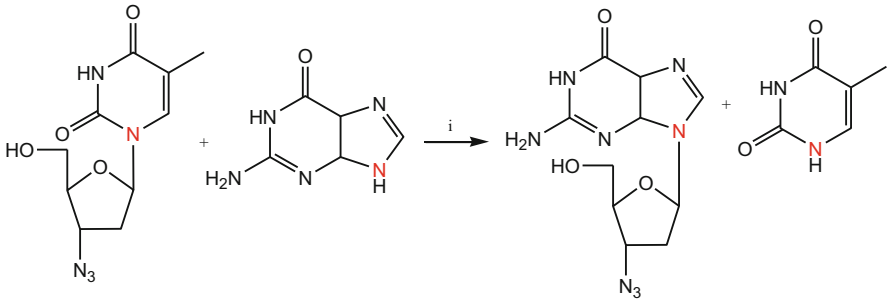
i) $Ph_3P{=}CHCO_2Et$, MeOH, 0°C. ii)HCldil. iii) t-Bu$(Me)_2$SiCl. imidazole, DMF. iv) LiN_3, THF, AcOH, H_2O. v) DIBAL, CH_2Cl_2, -78°C. vi)A c_2O,Py. vii) TMS-triflate, $ClCH_2CH_2Cl$. viii) n-Bu_4NF, THF.

Scheme 4.18 Synthesis of AZT from mannitol



i) PhCOCl (2.2equiv.), NEt_3, DMAP, CH_2Cl_2. b) $(CH_3)_3SiOTf$, $ClCH_2CH_2Cl$. c) NaOH (2equiv.), MeOH.
b) 4.7 NH_2SO_4 in MeOH.

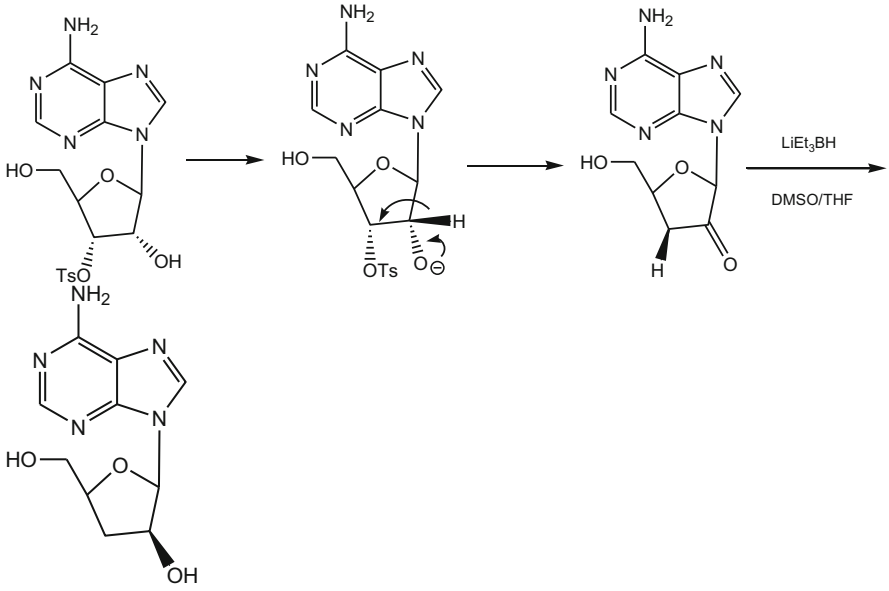
Scheme 4.19 Synthesis of AZT from azido diol intermediate



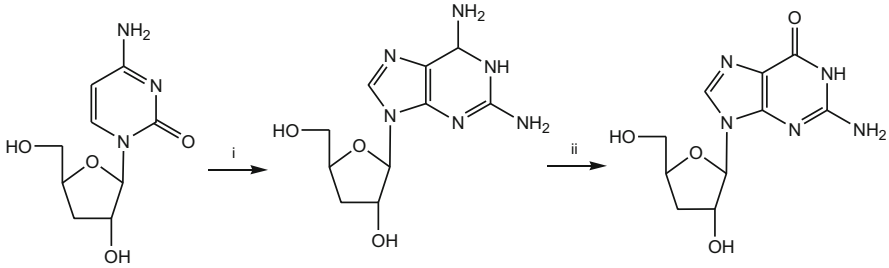
i) glycosyltransferases, pH6.0, 50°C.

Scheme 4.20 Enzymatic synthesis of 3′-azido-2′,3′-dideoxyguanosine

trifluoromethanesulfonate. Fluorination proceeds smoothly with 6 equiv. of $Et_3N.{}_3HF$ at reflux in 88% yield. Simultaneous 6-amination and 3′-debenzoylation was done with ammonia in high yield. Elimination of the 3′-hydroxy group was carried out under the Barton-McCombie procedure involving the formation of the 3′-O-thiocarbonyl followed by silane treatment. Final removal of trityl group provided FddA (Scheme 4.23) [60].



Scheme 4.21 Method for preparation of 3′-deoxynucleoside



i) 2,6-diaminopurine, *E. coli* BM-11 and BMT-4D/1A, K-phosphate buffer, 52°C, 26 h, 64%. ii) Adenosine deaminase (ADase), r.t., 16h, 68%.

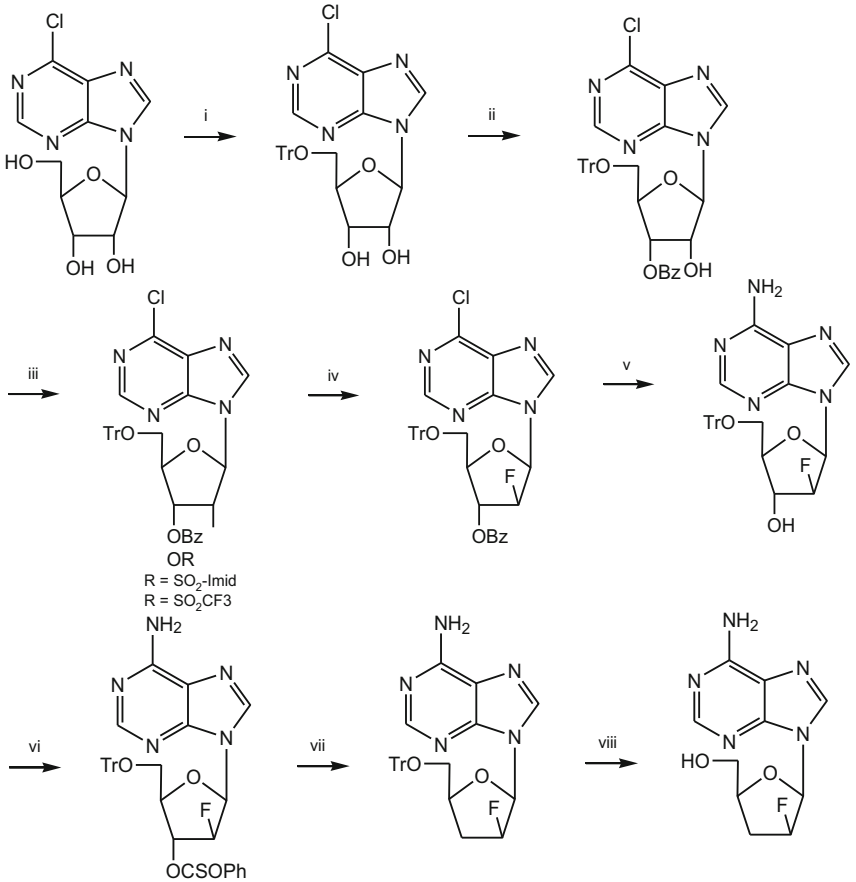
Scheme 4.22 Enzymatic synthesis of 3′-deoxyguanoside

4.1.2.4 4′-substituted Nucleosides

4′-substituted nucleosides have attracted much attention because of the discovery of potent anti-HIV agents 4′-azido- and 4′-cyano thymidine (Scheme 4.24).

One procedure involves the epoxidation of the exoglycal with dimethyldioxirane and ring opening of the resulting 4′,5′-epoxynucleosides to produce with high stereoselectivity the 4′-C-branched nucleosides (Scheme 4.25) [61].

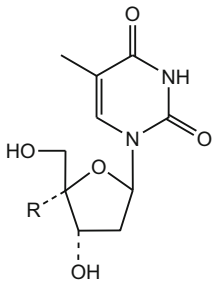
Likewise, others 4′-substituted nucleosides such as 4′-C-Ethynyl-β-D-arabino- and 4′-C-Ethynyl-2′-deoxy-β-D-ribopentofuranosyl pyrimidines have been reported by a different approach outlined in Scheme 4.26 [62].



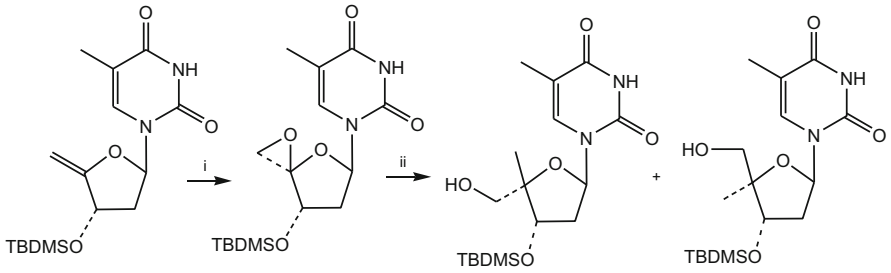
i) TrCl-iPrNH, DMF, 79%. ii) a) BzCl-Py, toluene. b) cat. Et_3N, toluene, 70%. iii) a) SO_2Cl_2-Py, CH_2Cl_2, b) imidazole. or CF_3SO_2Cl, DMAP, toluene. iv) Et_3.3HF, Et_3N, 70 and 78%. v) NH_3-MeOH, toluene 98%. vi) ClC(S)(OPh), DMAP, CH_3CN, 92%. vii) Ph_2SiH_2, AIBN, dioxane, 81%. viii) 80% AcOH, 100°C, 85%.

Scheme 4.23 Preparation of antiviral 2′3′-fluoro dideoxyadenosine FddA

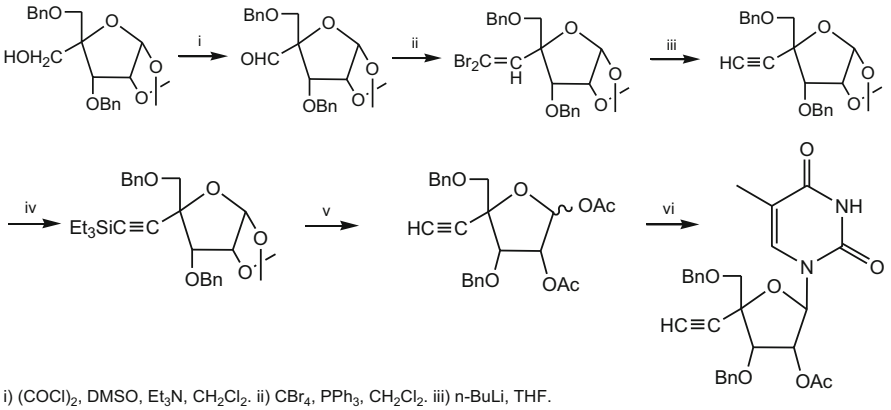
Scheme 4.24 Structure of potent anti-HIV 4′-substituted nucleosides



R = N_3, CN



Scheme 4.25 Ring opening of 4′,5′-epoxynucleosides

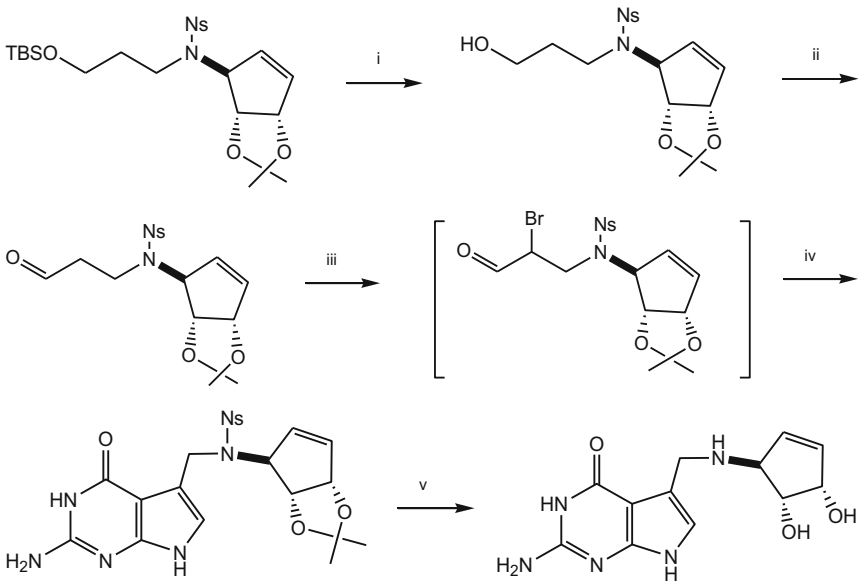


Scheme 4.26 Synthesis of 4′-C-Ethynyl-β-D-arabino- and 4′-C-Ethynyl-2′-deoxy-β-D-ribopentofuranosyl pyrimidines

4.1.3 Complex Nucleosides

The hypermodified Q base Queuine found in tRNA of plants and animals has been strongly associated with tumor growth inhibition. Three different approaches for preparing queuine have been described [63–65], the more recent in 11 steps from ribose. Completion of the synthesis involved the condensation of bromo aldehyde intermediate with 2,3-diamino-6-hydroxypyrimidine to give the desired heterocyclic product in 45 %. Final removal of protecting groups provided Q base (Scheme 4.27).

Capuramycin is a complex nucleoside antibiotic isolated from *Streptomyces griseus* 446-S3, which exhibit antibacterial activity against *Streptococcus pneumoniae* and



i) TBAF, THF, 87%. ii) TEMPO, NaOCl, KBr, CH_2Cl_2, 88%. iii) TMSBr, DMSO, MeCN. iv) NaOAc, H_2O/MeCN, 45%. v) a) $HSCH_2CH_2OH$, DBU, DMF, 46%. b) HCl, MeOH, 84%.

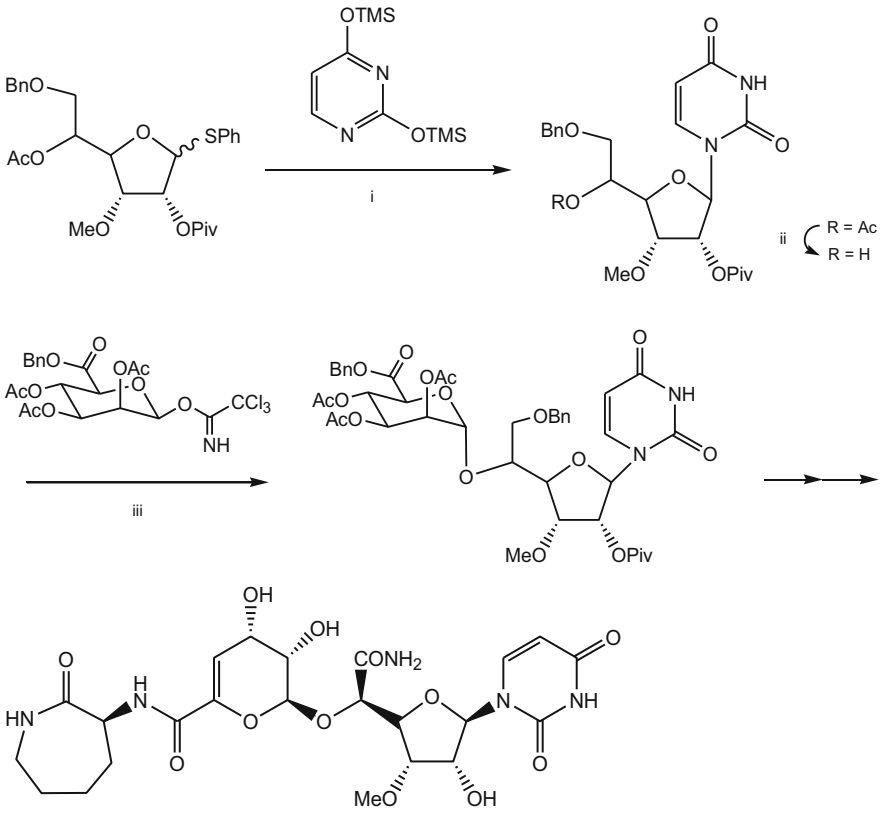
Scheme 4.27 Synthesis of hypermodified base Queuine

Mycobacterium smegmatis ATCC 607. The total synthesis was reported by Knapp and Nandan [66] consisting in the glycosylation reaction between the key thioglycoside donor and silylated pyrimidine to produce the corresponding L-*talo*-uridine. The next glycosidic coupling reaction was carried out with L-*talo*-uridine and imidate glycosyl donor under TMS-OTf conditions to provide the disaccharide nucleoside. Further transformations lead to the target molecule (Scheme 4.28).

Due its promising role as anti-tuberculosis drug, further efforts for preparing capuramycin and other analogs have been deployed as described in a more recent concise total synthesis [67].

Moreover, capuramycin has been also chemically transformed in an attempt to extend the antibacterial spectrum. Thus, radical oxygenation gave unexpected lactone in moderate yield via an intramolecular radical Ar-C glycosylation-lactonization reaction (Scheme 4.29) [68].

Synthetic studies of unique class tunicamycin antibiotics leading to the preparation of (+)-tunicaminyluracil, (+)-tunicamycin-V, and 5′-*epi*-tunicamacyn-V were described by Myers et al. [69] The key features are the development and application of a silicon-mediated reductive coupling of aldehydes, the allylic alcohols to construct the undecose core of the natural product, and the development of an efficient procedure for the synthesis of the trehalose glycosidic bond within the antibiotic (Scheme 4.30).



i) NIS, TfOH, CH_2Cl_2, -20°C. ii) NaOMe, MeOH, 77%. iii) TMS-OTf, CH_2Cl_2, -25°C, 16h, 85%.

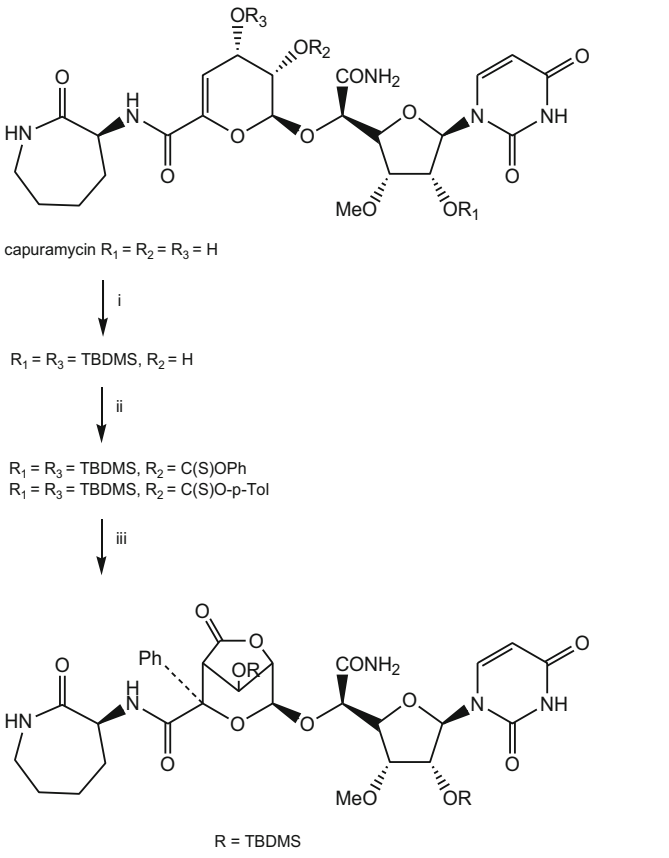
Scheme 4.28 Synthesis of Capuramycin

An alternative approach for the synthesis of tunicamycins is reported in a stereoselective approach, the key reactions being the Mukaiyama aldol reaction, intramolecular acetal formation, gold(I)-catalyzed O- and N-glycosylation, and final N-acylation (Scheme 4.31) [70].

4.1.3.1 Fused Heterocyclic Nucleosides

Selective and potent anti-Varicella Zoster Virus (VZV) bicyclic furanopyrimidine deoxynucleosides were synthesized. The bicyclic formation was performed by palladium-catalyzed coupling of aryl acetylenes with 5-iodo-2′-deoxyridine providing the desired fused furan nucleoside (Scheme 4.32) [71].

Triciribine is a tricyclic nucleoside with antineoplastic and antiviral properties, synthesized in an improved fashion from 6-bromo-5-cyanopyrrolo [2,3-d] pyrimidin-

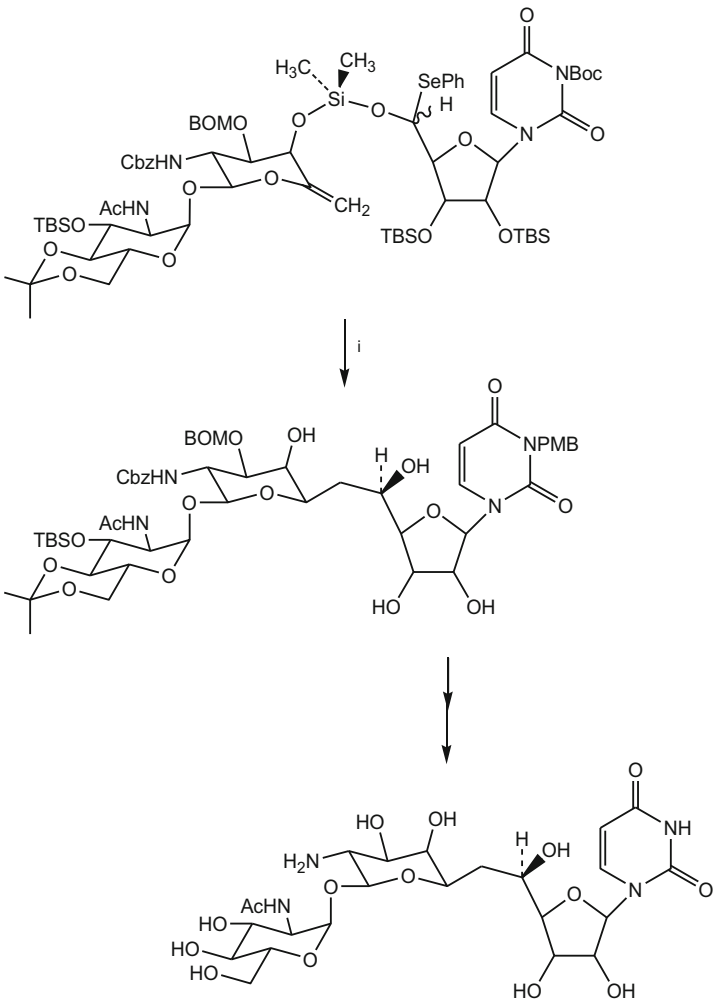


Scheme 4.29 Chemical transformations of capuramycin

4-one intermediate. A series of transformations including *N*-glycoside coupling reaction provided 4-amino-5-cyano-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosy] pyrrolo [2,3-d] pyrimidine that was then converted to the desired tricyclic nucleoside (Scheme 4.33) [72].

4.2 *C*-nucleosides

These modified nucleosides are structurally distinct to their counterparts *N*-nucleosides because of the presence of a C-C linkage instead of C-N between the furanoside and the heterocyclic aglycon. Their source could be either naturally occurring (pyrazomycin, showdomycin, formycin) or synthetic (thiazofurin),

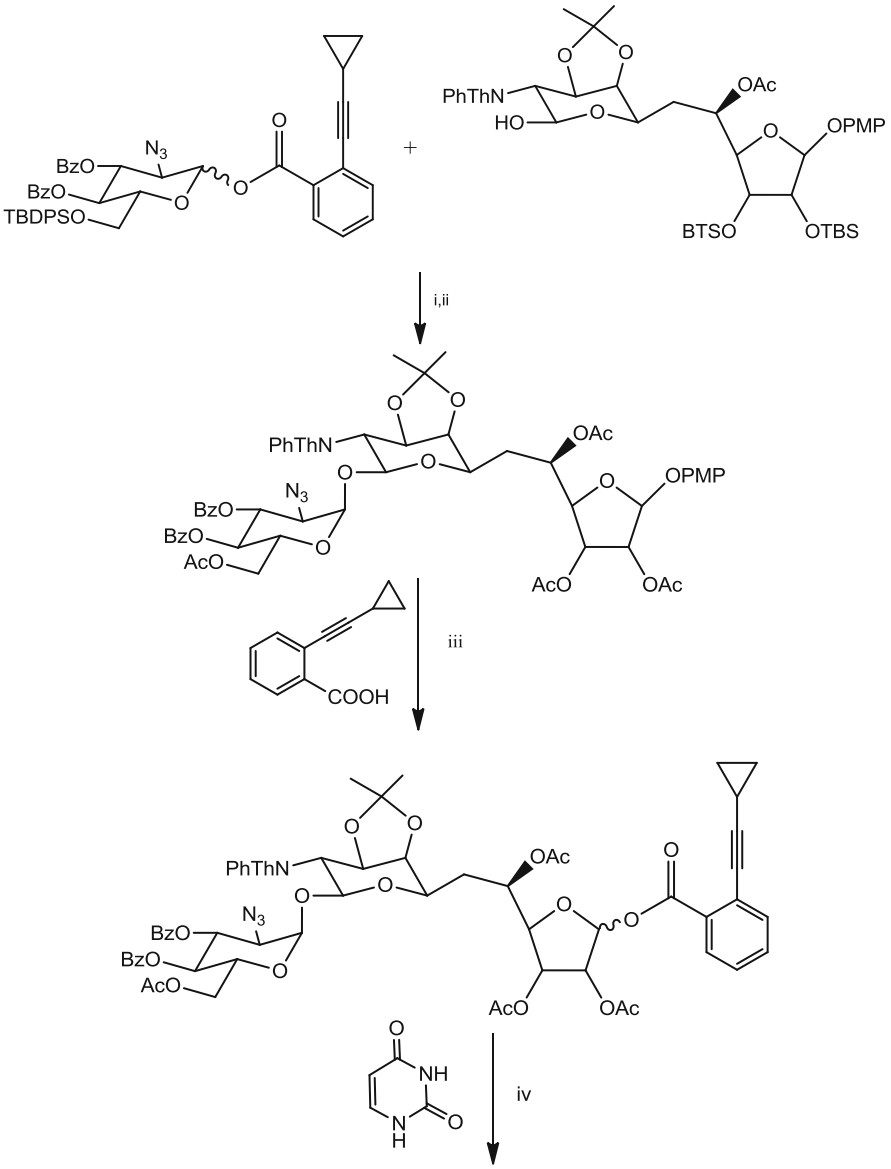


Scheme 4.30 Key step for the synthesis of Tunicamycin antibiotic

having in either case significant antitumor and antiviral activity. Also, some of them have been found in tRNA codons (pseudouridine) and others (tiazofurin and oxazofurin) designed as competitive inhibitor of cofactor nicotinamide adenine dinucleotide (Scheme 4.34).

An early approximation for the preparation of *C*-nucleosides proposed two basic possibilities depending on the nature of the atoms surrounding the C–C bond (Scheme 4.35) [73].

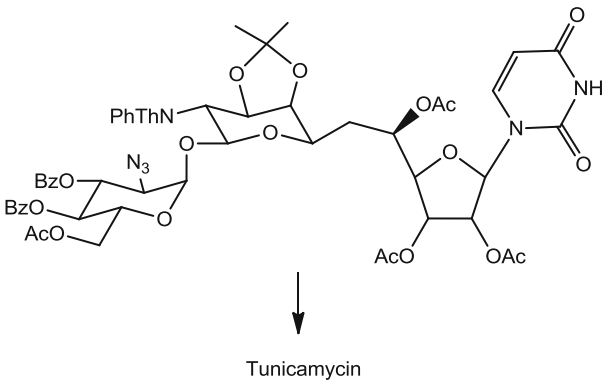
(a) If there is one heteroatom adjacent to the *C*-glycosidic bond, for example tiazofurin, formycin, Pyrazomycin.
(b) If there is no heteroatom adjacent to the *C*-glycosidic bond.



Scheme 4.31 Synthesis of tunicamycins mediated by gold complex catalysis

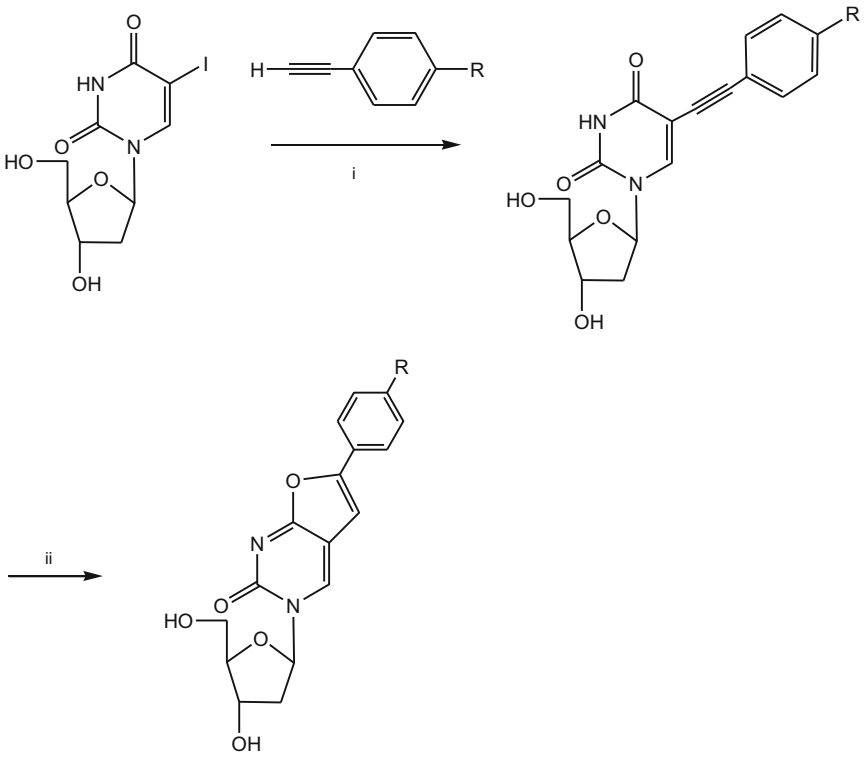
Alternatively other authors consider three general pathways for preparing *C*-nucleosides depending on the precursor employed as starting material [74].

An early synthesis of modified *C*-nucleoside from naturally occurring pseudouridine was carried out via ring opening with ozone to generate intermediate which was treated with thiosemicarbazone to provide 6-azathiopseudouridine. Treatment with iodomethane in acid medium produces the desired *C*-nucleoside as shown in Scheme 4.36 [75].



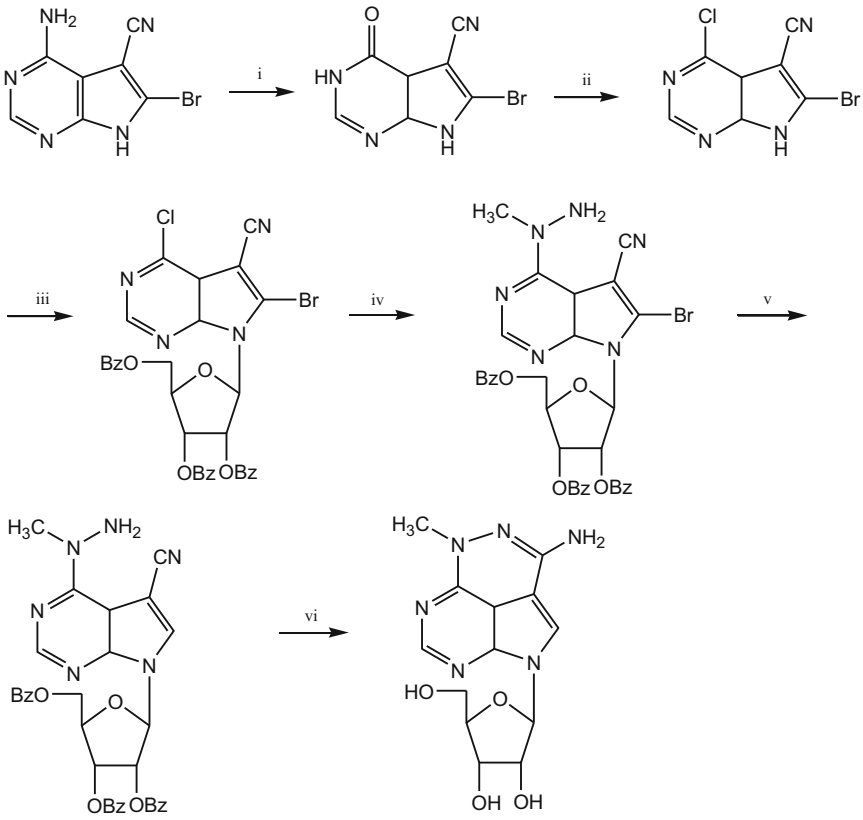
i)[$Ph_3PAuNTf_2$], toluene, AW MS, RT.i) a) HF.Pyr, THF, 60°C. b) Ac_2O, Pyr, DMAP, RT.iii) a) CAN, THF/H_2O, RT. b) EDCl, DMAP, DIPEA, DCM, RT. iv) a) BSTFA, CH_3CN, 50°C. b) [$Ph_3PAuNTf_2$], $ClCH_2CH_2Cl$, RT.

Scheme 4.31 (continued)



i) $Pd(PPh_3)_4$, iPr_2EtN, CuI, DMF, r.t, 19h. ii) Et_3N/MeOH. CuI, Δ, 4h.

Scheme 4.32 Synthesis of bicyclic furano pyrimidine



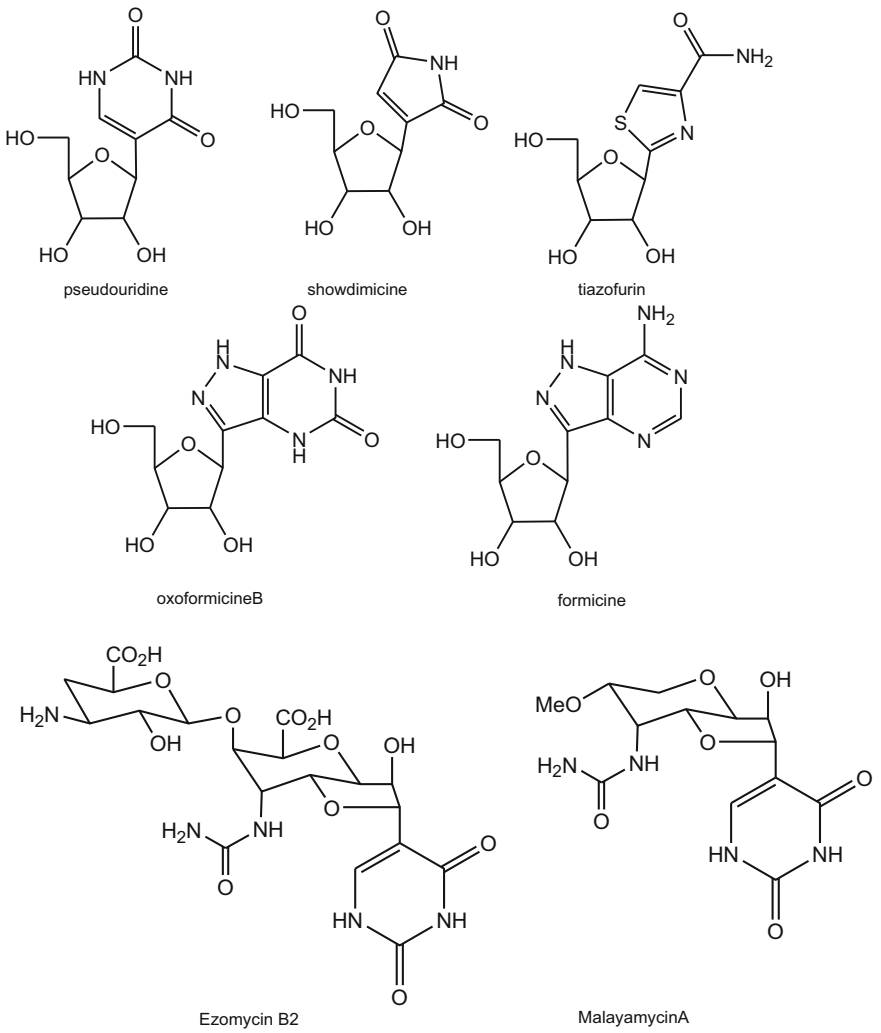
i) $NaNO_2$, AcOH, H_2O, ii) $POCl_3$. iii) BSA, CH_3CN then 1-O-acetyl-2,3,5-tri-O-benzoyl-b-D-ribofuranoside, TMSOTf. iv) NH_2NHCH_3, EtOH, $CHCl_3$. v) HCO_2NH_4, 10% Pd-C, EtOH, reflux. vi) NaOMe, MeOH, reflux.

Scheme 4.33 Synthesis of tricyclic nucleoside Triciribine

The synthesis of the *C*-nucleoside pseudouridine was reported by Asburn and Binkley [76], involving the condensation between 5-*O*-acetyl-2,3-*O*-isopropylidene-D-ribonolactone and 2,4-dibenzyloxypyrimidin-5-il lithium to provide the condensation product which was subjected to hydride reduction and hydrogenolysis to yield pseudouridine (Scheme 4.37).

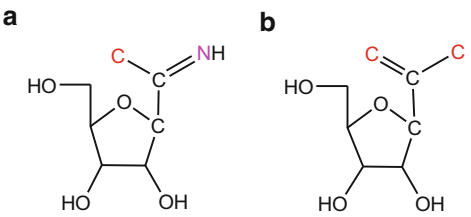
Antitumor *C*-nucleoside tiazofurin was synthesized by Robins et al. [77], from 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide which undergoes ring closure under conditions described in Scheme 4.38.

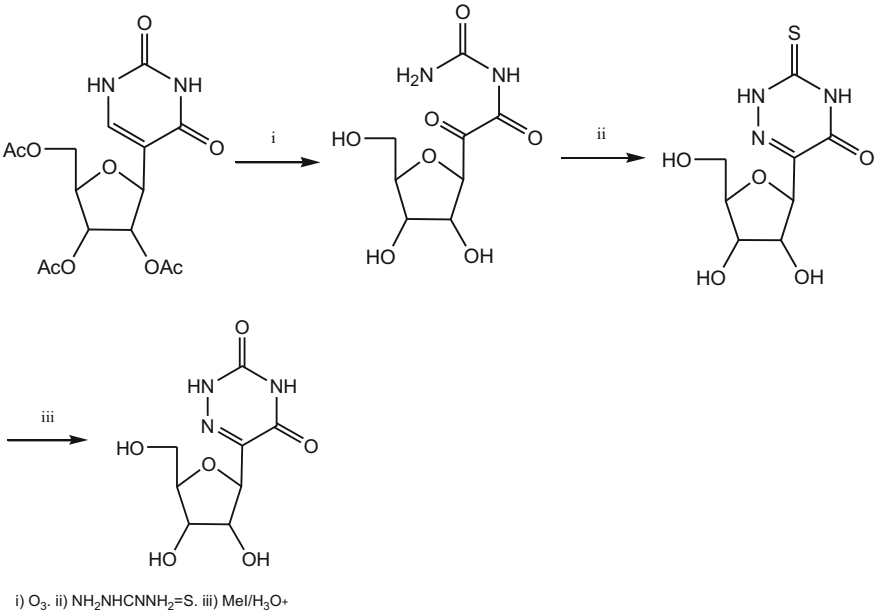
A new report for the synthesis of Tiazofurin is described, avoiding the use of H_2S gas which is unsafe on large-scale production. The synthesis initiate with the preparation of 1-cyano-2,3-*O*-isopropylidene-5-*O*-benzoyl-β-D-ribofuranose which was reacted with cysteine ethyl ester hydrochloride to give thiazoline derivative in 90 %. Further steps including oxidative aromatization under MnO_2 in



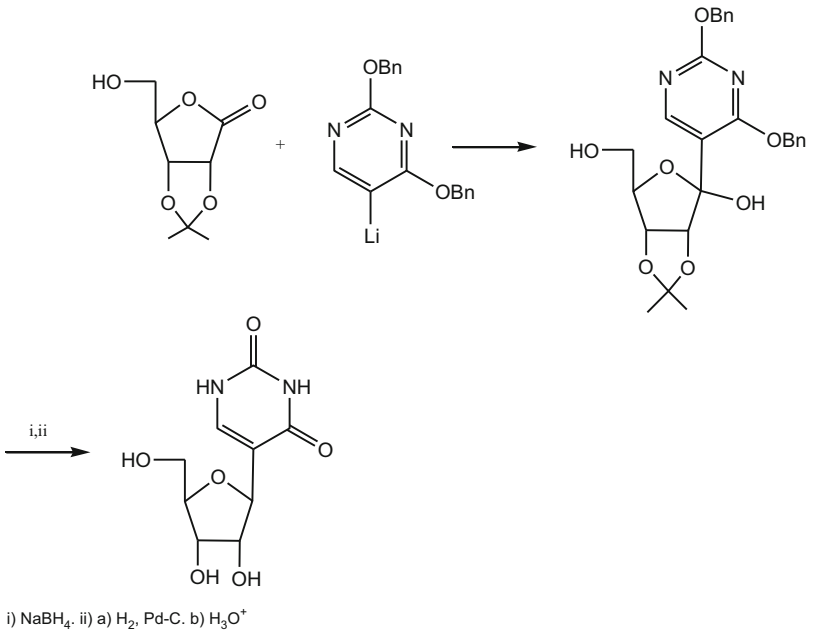
Scheme 4.34 Biologically active *C*-nucleosides

Scheme 4.35 *C*-nucleosides partial representations, with and without heteroatom attached to the *C*-glycosidic bond

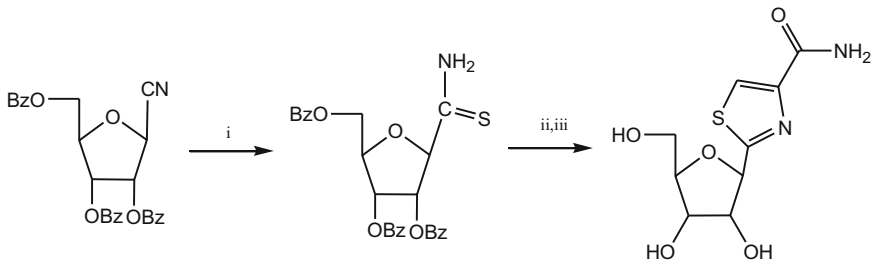




Scheme 4.36 Preparation of 6-azapseudouridine

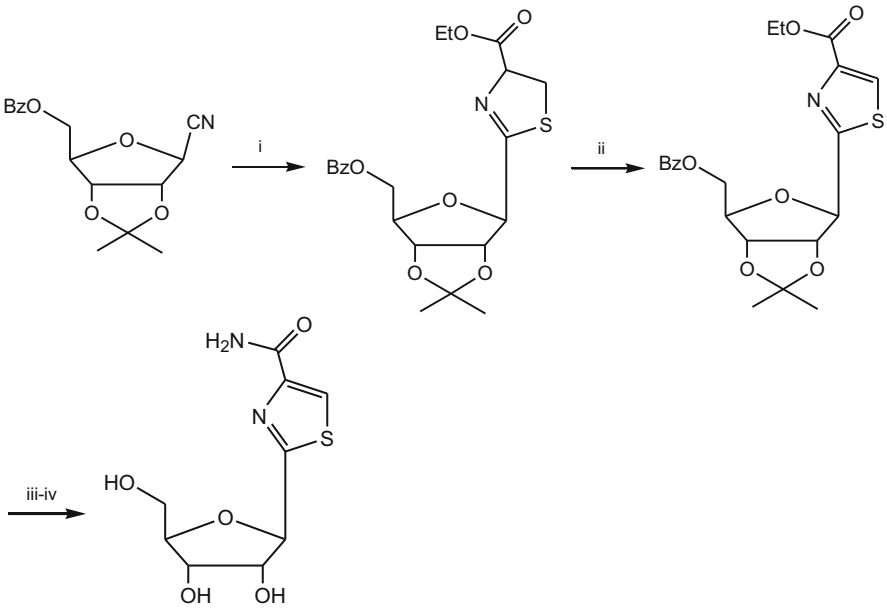


Scheme 4.37 Preparation of pseudouridine



i) H_2S, 4-DMAP. ii) ethylbromopyruvate. iii) NH_3/MeOH.

Scheme 4.38 Synthesis of tiazofurin



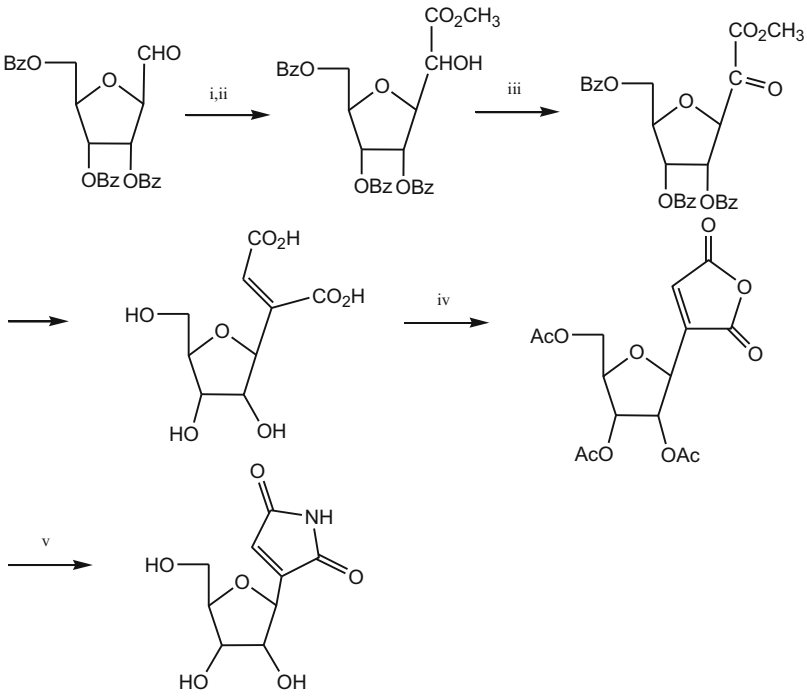
i) Cysteine ether ester hydrochloride/TEA. ii) MnO_2/Ph, reflux. iii) 90% TFA. iv) MeOH/NH_3

Scheme 4.39 A new synthetic methodology for tiazofurin

benzene and acetonide deprotection with iodide in methanol produced the desired *C*-nucleoside (Scheme 4.39) [78].

Another biologically important *C*-nucleoside known as showdomycin was prepared by Trumnlitz and Moffat [79]. The aldehyde used as starting material was converted first to an α-hydroxyacid and then to α-ketoacid. Wittig reaction on this intermediate and Lewis acid catalysis produced ring closure (Scheme 4.40).

Pyrazine riboside derivative was synthesized by treatment of glycine riboside with formaldehyde and cyanide (Strecker conditions) to generate cyanide intermediate as a mixture of isomers. Sulfenylation and sodium methoxide treatment produce the *C*-nucleoside (Scheme 4.41) [80].



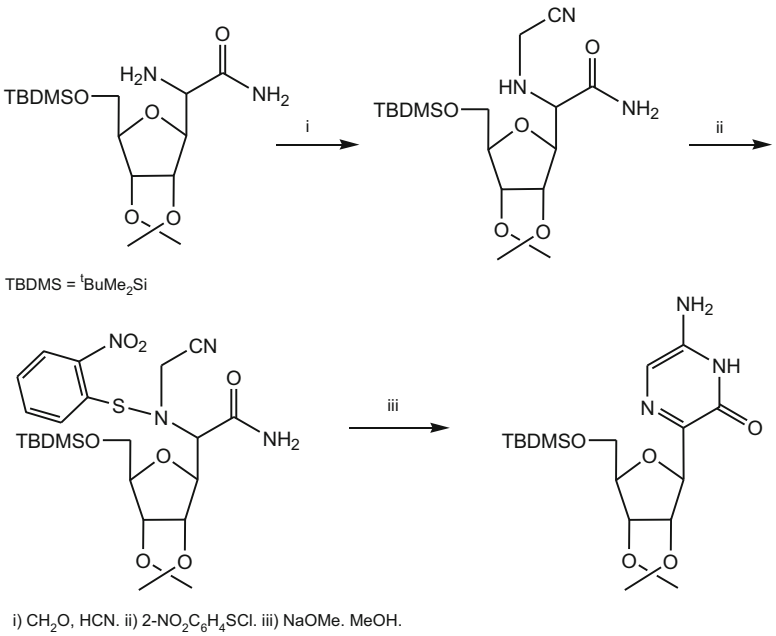
i) NaCN. ii) a) MeOH-H_3O^+. b) Me_2SO-DCC. iii) $Ph_3P{=}CHCONH_2$. iv) Ac_2O. v) a) NH_3. b) EPP. v) H^+.

Scheme 4.40 Preparation of showdomycin

Analogs of antiviral *C*-nucleoside Formycin have been synthesized by using the palladium-mediated glycosidic reaction between the furanoid glycal and the iodinated heterocycle. Similar conditions were used for preparing the pyrimidine analogs (Scheme 4.42) [81].

Radical cyclization of ribo-phenylselenoglycoside tethered with propargyl moieties on C-5 hydroxyl group provided cyclic intermediates potentially useful for the synthesis of *C*-nucleoside derivatives. Propargyl intermediate was prepared from ribo-phenylselenoglycoside via two-step sequence and then under radical reaction conditions (Bu_3SnH/AIBN) transformed to the cyclic intermediates in high yields. Further ring opening produce aldehyde intermediate which was subjected to coupling reaction with 1,2-phenylenediamine to produce the pyrazine *C*-glycoside (Scheme 4.43) [82].

Polyhalogenated quinoline *C*-nucleosides were synthesized as potential antiviral agents. The key step reaction for quinolin-2-one ring formation consisted in the condensation between 2-aminophenone allose derivative and keteneylidene(triphenyl)-phosphorane in benzene under reflux to provide the desired 6,7-dichloroquinolin-2-one nucleoside in 50 % yield (Scheme 4.44) [83].



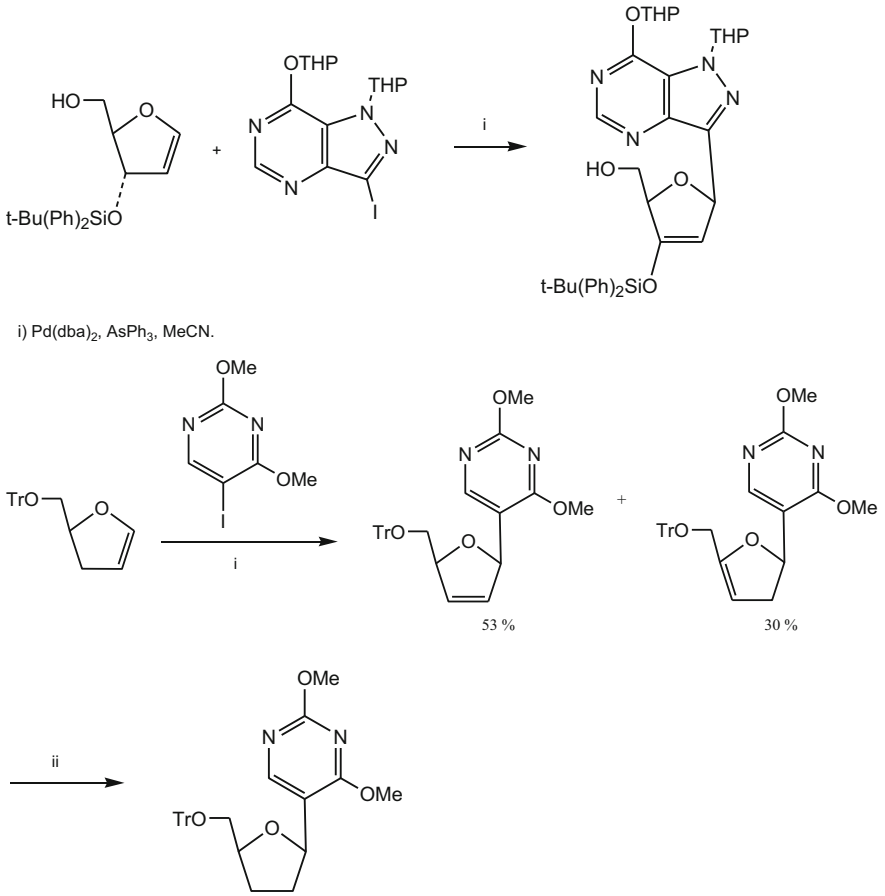
Scheme 4.41 Synthesis of *C*-nucleoside by pyrazine ring formation

The novel bicyclic *C*-nucleoside malayamycin A from *Streptomyces malaysiensis* was elegantly synthesized from D-ribonolactone which was transformed to the target molecule according to the pathway indicated in Scheme 4.45 [84].

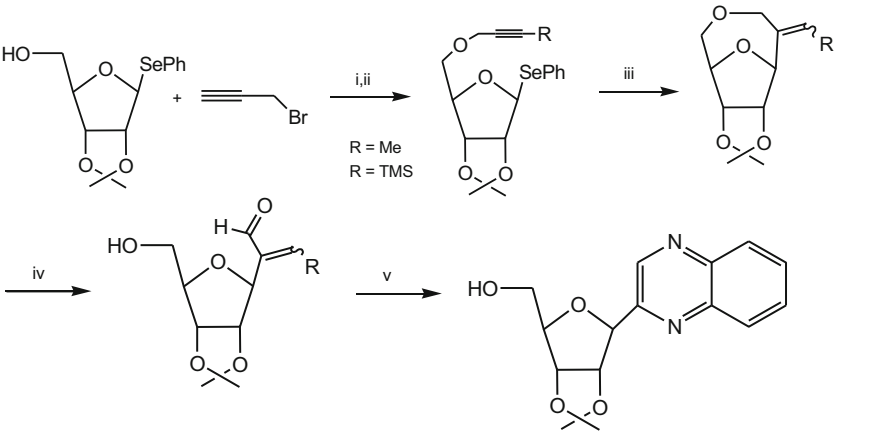
4.3 Carbocyclic Nucleosides

This class of modified nucleosides in which the furanose ring has been replaced by a cycloalkane ring (mainly cyclopentane) has been prepared by chemical or enzymatic methods. Besides their potent antitumor and antiviral activity for some of them, they have also shown high resistance to phosphorylases.

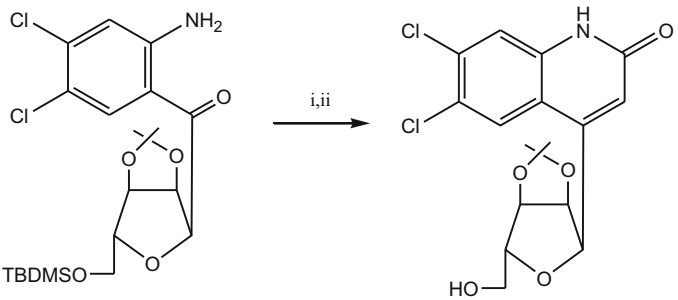
The use of enzymes particularly lipases for protections and deprotections is an important strategy for preparing carbocyclic nucleosides. This approach has been advantageous especially for the resolution of enantiomeric forms, leading to high enantiomeric purity. Constrained three [85] and four [86] member ring carbocyclic nucleosides have been obtained by applying chemoenzymatic methodologies involving lipase for enantiomeric resolution and stereoselective deprotections. In the case of more abundant five member rings the use of lipases for enzymatic resolution and regioselective deprotections have been under intense study. Special attention has been paid to cyclopentenyl diacetates which have been used as building blocks for the preparation of important carbocyclic nucleosides such as Neplanocin and Aristeromycin. To achieve this goal, the hydrolase enzyme acetyl-cholinesterase



Scheme 4.42 Palladium-mediated synthesis of *C*-nucleoside formycin analogs

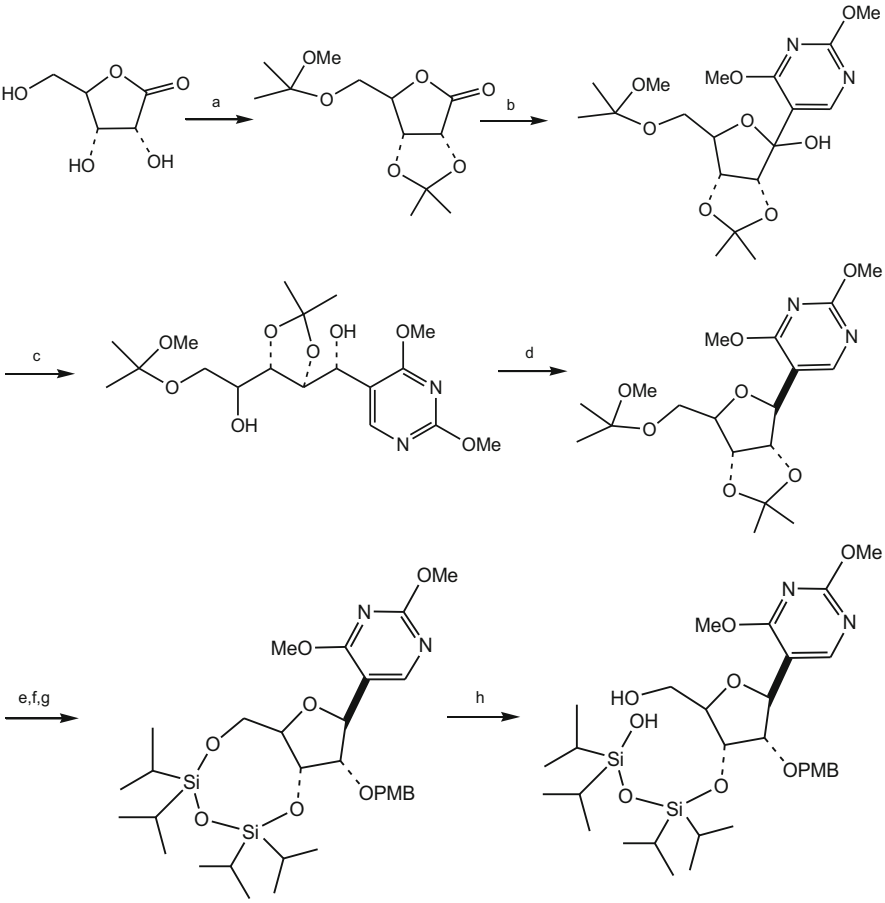


Scheme 4.43 *C*-nucleoside derivative formation via radical cyclization

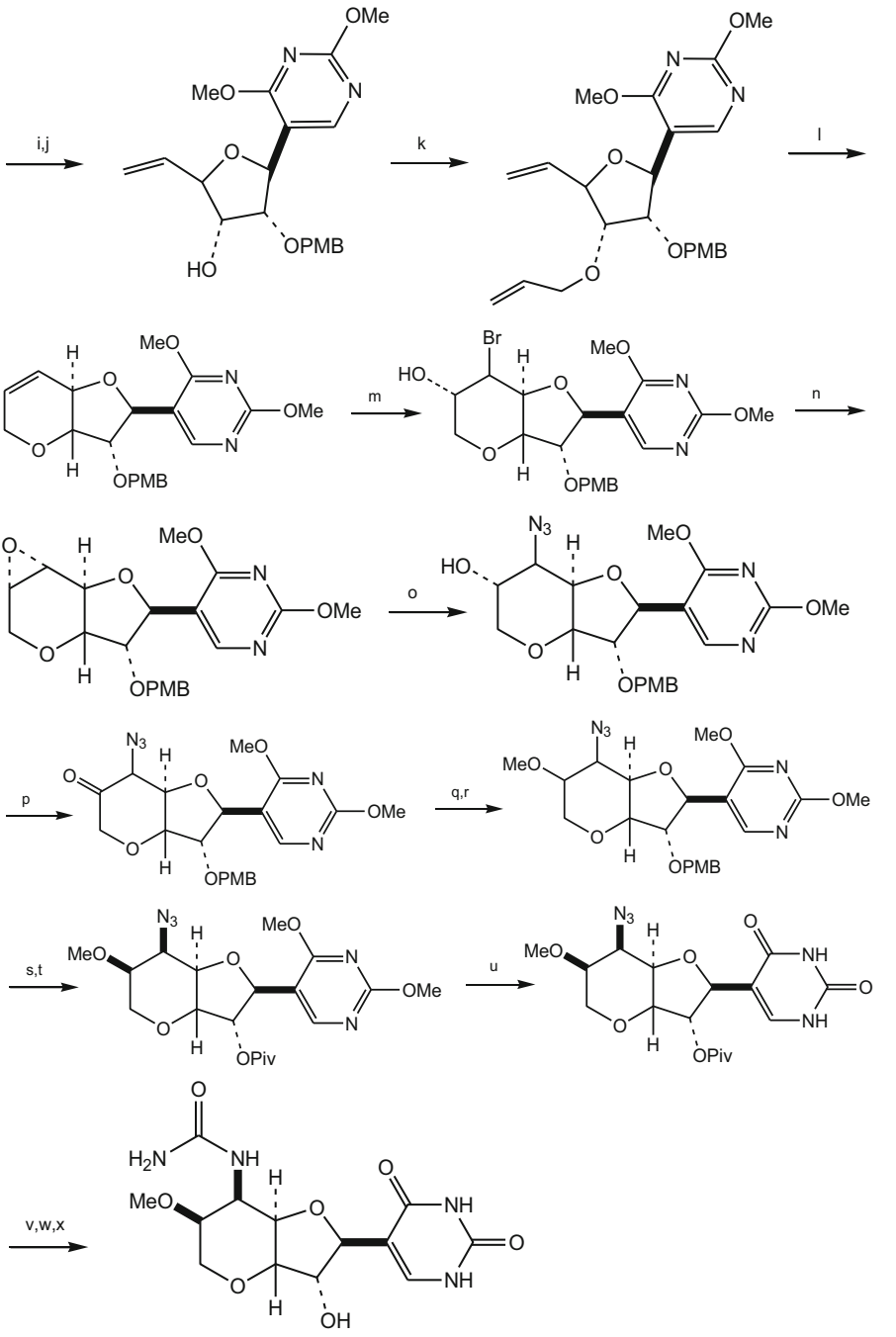


i) $Ph_3P{=}C{=}C{=}O$, PhH, reflux. ii) TBAF, THF, rt.

Scheme 4.44 Quinolin-2-one *C*-nucleoside formation via Wittig reaction



Scheme 4.45 Total synthesis of *C*-nucleoside Malayamycin A

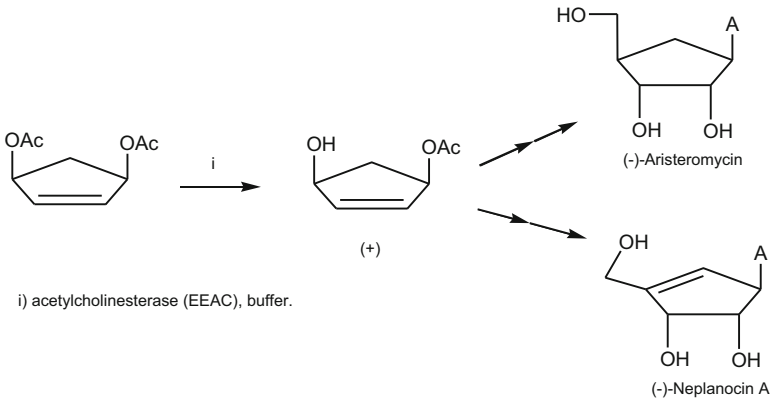


Scheme 4.45 (continued)

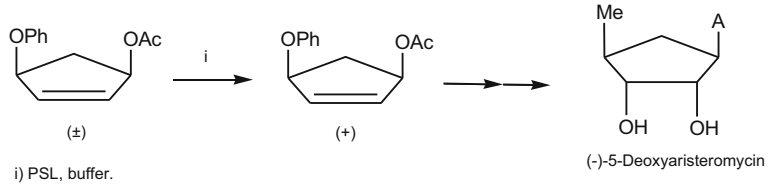
(EEAC) [86] showed high efficiency for obtaining the desired enantiomer (1R,4S)-4-hydroxy-2-cyclopentenyl derivative in enantiomeric excess (ee) up to 96% (Scheme 4.46) [87–89].

Racemic cyclopentenyl derivatives have been used as starting material in the preparation of the antiviral carbocyclic nucleoside (−)-5′-deoxyaristeromycin. The key step reaction was the enzymatic resolution with *Pseudomonas* sp. lipase (PSL) of the racemic mixture providing the (+)-enantiomer which was transformed chemically to the desired carbocyclic nucleoside (Scheme 4.47).

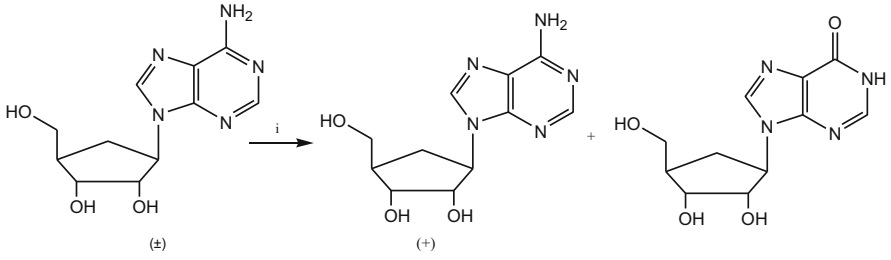
The separation of racemic carbocyclic nucleosides by enzymatic means has been reported as an alternative approach. Thus, racemic aristeromycin was treated with adenosine deaminase (ADA) to give (−)-carbocyclic inosine and pure dextrorotatory enantiomer (Scheme 4.48) [90].



Scheme 4.46 Enantiomeric resolution of prochiral cyclopentene diacetate



Scheme 4.47 Enzymatic resolution of racemic cyclopentene building blocks



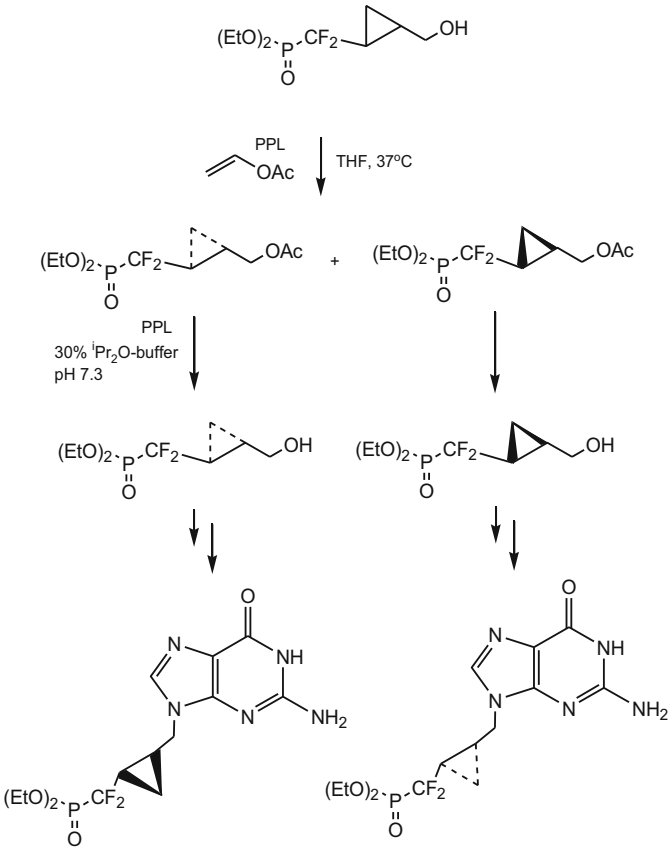
Scheme 4.48 Enzymatic resolution of carbocyclic nucleoside

4.3.1 Cyclopropane Carbocyclic Nucleosides

Conformationally constrained cyclopropane nucleosides have been prepared following a chemoenzymatic approach [85]. Thus, the racemic resolution of *trans*-1-(diethoxyphosphyl)difluoromethyl-2-hydroxymethylcyclopropane followed by acetate hydrolysis was carried out with porcine pancreas lipase (PPL) to yield (+)- and (−)-cyclopropanes in high enantiomeric excess. Further transformation lead to the preparation of the target cyclopropane nucleoside (Scheme 4.49).

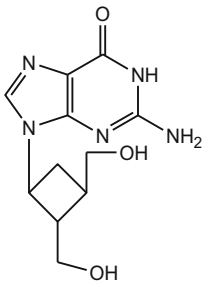
4.3.2 Cyclobutane Carbocyclic Nucleosides

Lubocavir is a synthetic potent inhibitor of DNA polymerase, active against cytomegalovirus [91] (Scheme 4.50).

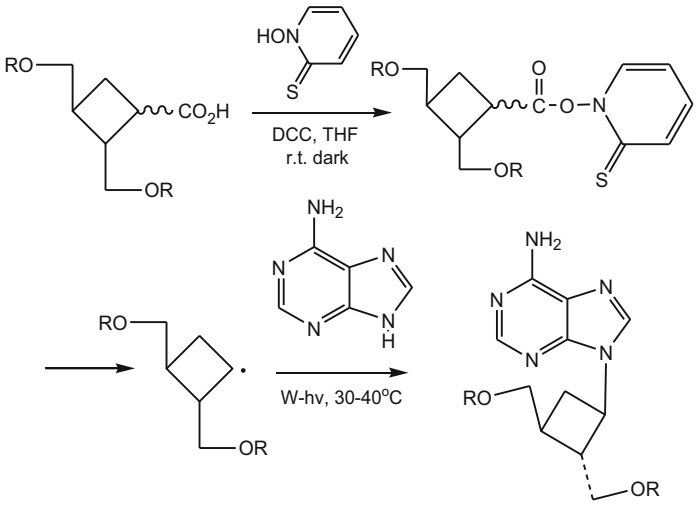


Scheme 4.49 Chemoenzymatic syntheses of cyclopropane nucleosides

Scheme 4.50 Structures of carboxetan carbocyclic nucleoside



Lobucavir



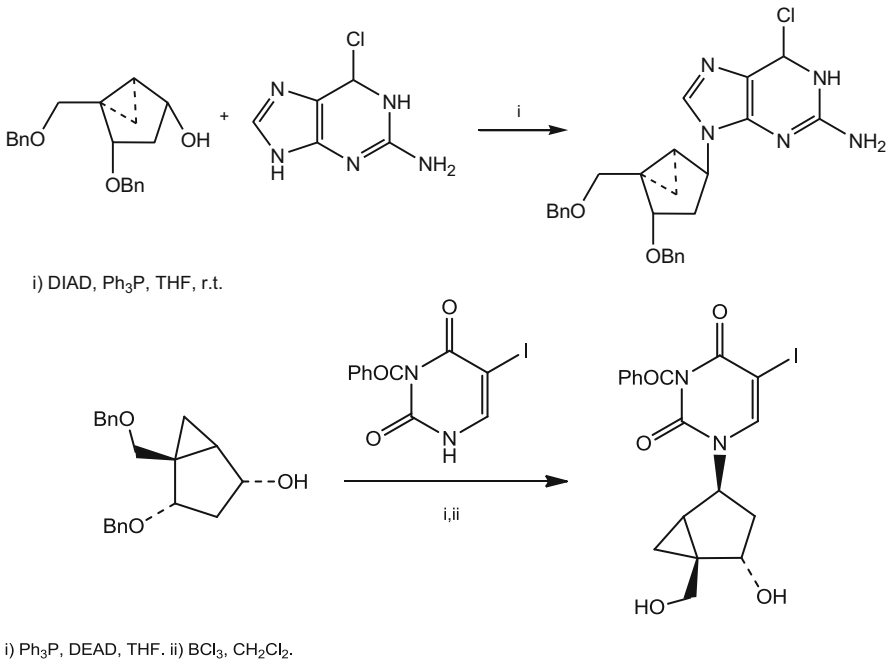
Scheme 4.51 The Barton decarboxylation method for the preparation of carbocyclic *C*-nucleosides

The carbocyclic four-membered *C*-nucleoside cyclobut-A was prepared following the Barton decarboxylation method. The method is based on the reaction between carboxylic acids and heteroaromatic compounds (Scheme 4.51) [92].

Other carbocyclic oxetanocin analogs have been prepared from oxetanocin A [93] 3,3-diethoxy-1,2-cyclobutanedicarboxylate [94], and enantiomeric cyclobutanone intermediates [95] as starting materials.

4.3.3 Cyclopentane Carbocyclic Nucleosides

The Mitsunobu reaction has become a valuable alternative approach for preparing cyclopentane carbocyclic nucleosides. This has been demonstrated in the preparation of conformationally locked carbocyclic AZT triphosphate analogs under these



Scheme 4.52 Synthesis of conformationally locked carbocyclic purine and pyrimidines under the Mitsunobu approach

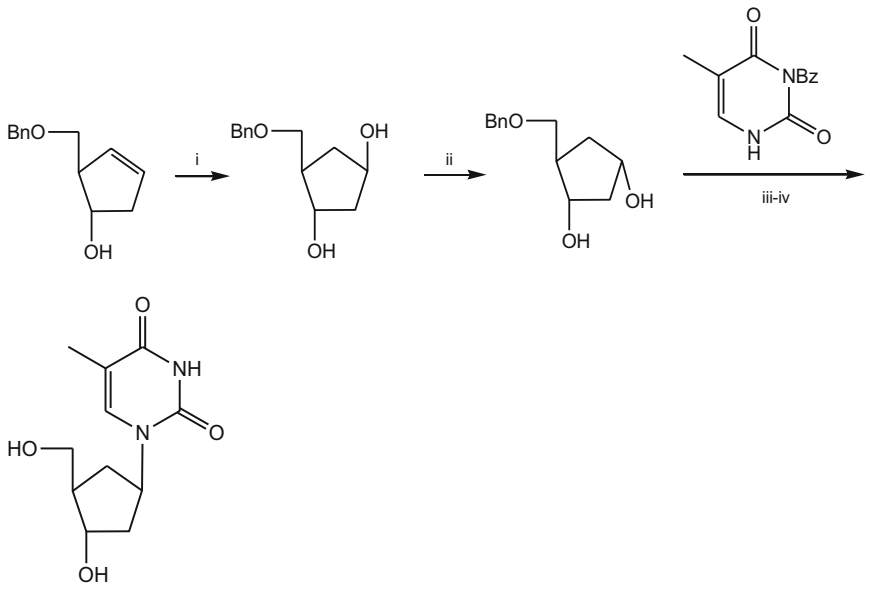
versatile conditions [96]. The standard procedure usually takes place with diethyl or diisipropylazocarboxylate (DEAD or DIAD) with triphenylphosphine $(Ph)_3P$ in THF to yield carbocyclic purines or pyrimidines nucleosides in high yield (Scheme 4.52) [97].

Another example on the applicability of this method was observed in the preparation of the carbocyclic thymidine nucleoside. It is worth mentioning that the desired stereochemistry of the hydroxyl group is obtained also through the Mitsunobu reaction (Scheme 4.53) [98].

4.3.4 Palladium Mediated

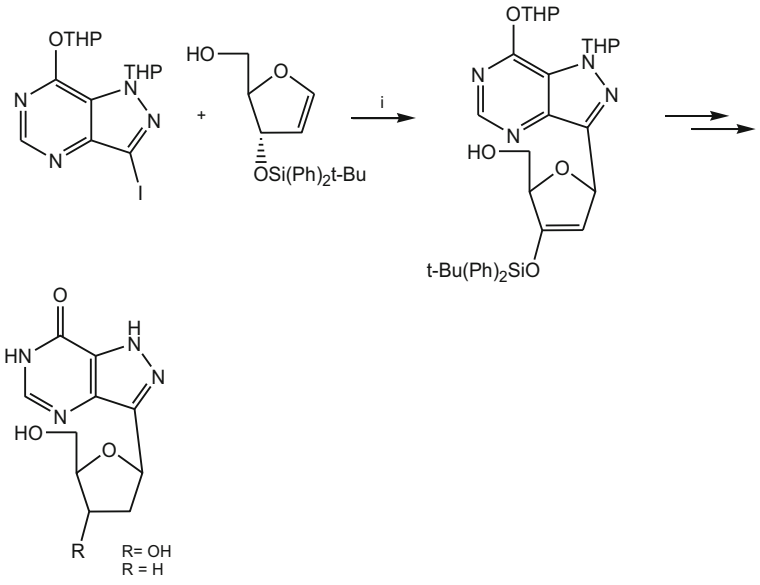
Based on the widespread palladium-coupling methodologies, several dideoxy, carbocyclic and *C*-nucleosides have been efficiently prepared. For instance the antiviral *C*-nucleosides 2′-deoxyformycin B was prepared by condensation reaction between the heterocycle iodide intermediate and the glycal, under $Pd(dba)_2$ as palladium catalyst in 62 % yield (Scheme 4.54) [99].

Solid phase synthesis of carbovir analogs under palladium catalysis was recently reported [100]. The carbocyclic derivative was linked to the Wang resin and then coupled with chloropurines under Pd(0) catalyst (Scheme 4.55).



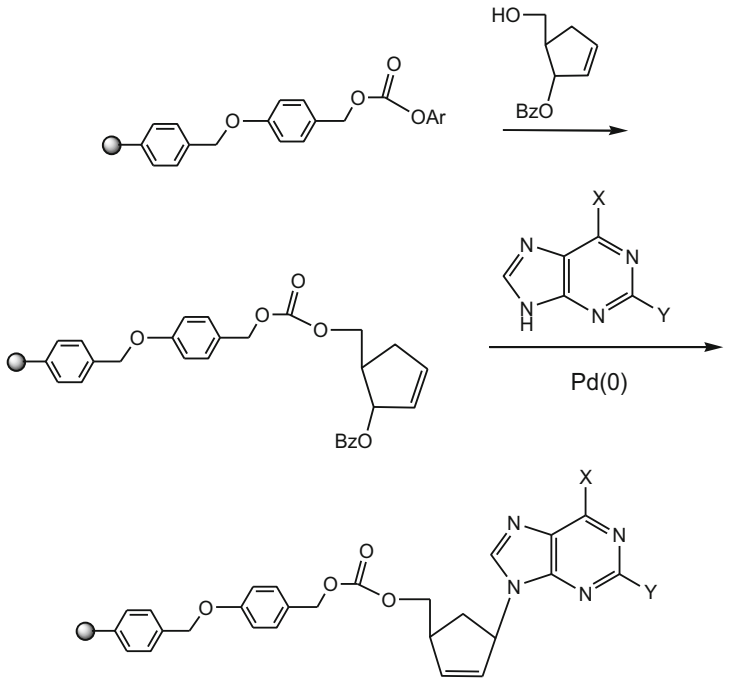
i) NaH, BnBr. ii) 9-BBN, H_2O_2/NaOH, 87%. iii) PPh_3, DIAD. iv) a) NaOH/MeOH. b) H_2, Pd/C, 90%

Scheme 4.53 The Mitsunobu reaction for preparation of the carbocyclic thymidine nucleoside

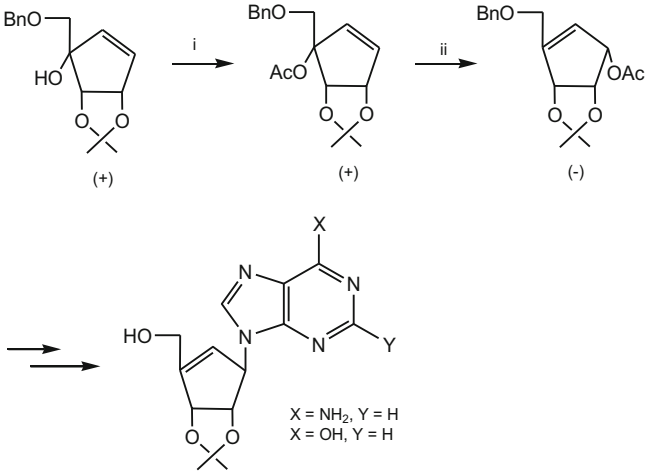


i) $Pd(dba)_2$, $AsPh_3$, CH_3CN.

Scheme 4.54 Palladium-mediated 2′-deoxyformycin B and 2′,3′-dideoxyformycin B

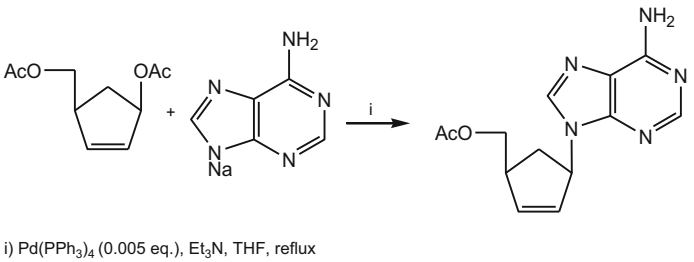


Scheme 4.55 Solid-phase synthesis of carbocyclic nucleosides under palladium catalysis

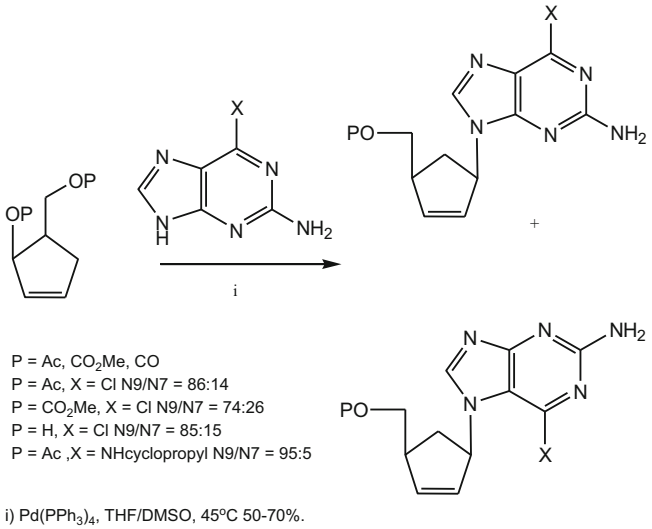


Scheme 4.56 Tsuji-Trost reaction for the preparation of neplanocin A

The Tsuji-Trost approach was used to prepare (−)-neplanocin A and its analog [101]. This synthesis proceeds via an allylic rearrangement of the hydroxyl group from the (+)-allylic alcohol to the (−)-allylic acetate (Scheme 4.56).



Scheme 4.57 Palladium catalyzed synthesis of aristeromycin

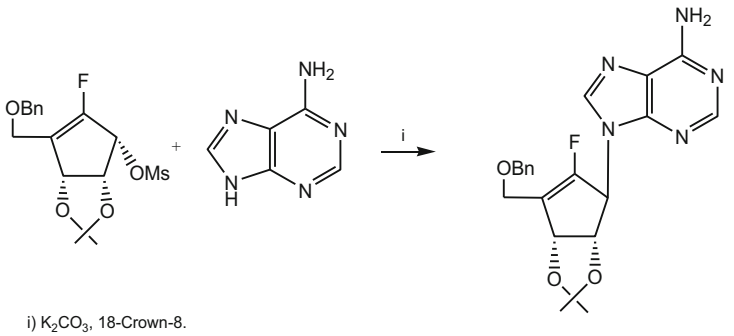


Scheme 4.58 Palladium-catalyzed coupling with purine base

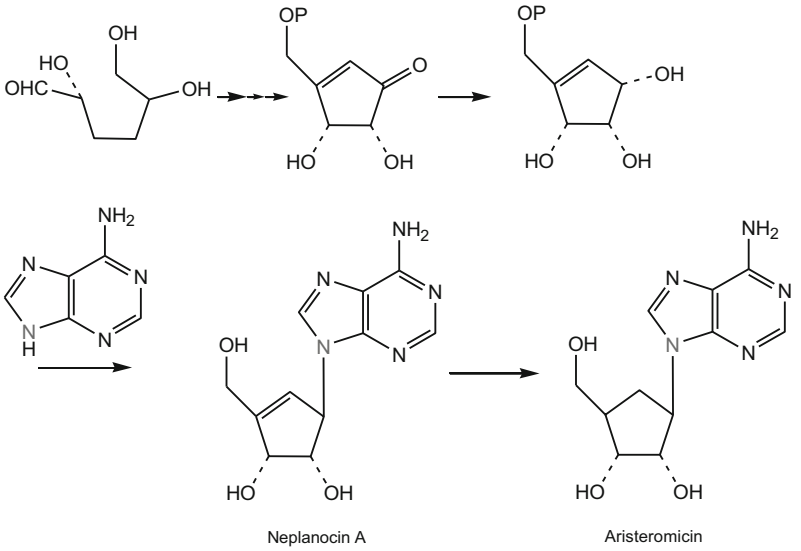
Carbocyclic nucleoside aristeromycin with antitumor and antiviral activity was prepared by condensation of the carbocyclic diacetate intermediate with the sodium salt of adenosine base under Pd(0) in 75 % yield (Scheme 4.57) [102].

Palladium mediated coupling of purine base with carbocyclic acetates, carbonates or benzoates lead to a mixture of N-7 and N-9 isomers. The regioselectivity of purine alkylations depends on the size and nature of the ligands, the most typical being Ph_3P, BINAP, $P(OMe)_3$, $P(OiPr)_3$, $P(OPh)_3$ (Scheme 4.58) [103].

Another straightforward methodology for preparing carbocyclic nucleosides involves the direct condensation of mesylated carbocyclic intermediate with the heterocyclic base in the presence of potassium carbonate and crown ethers as coupling conditions (Scheme 4.59) [104].



Scheme 4.59 Preparation of carbocyclic nucleosides with mesylated carbocyclic intermediates

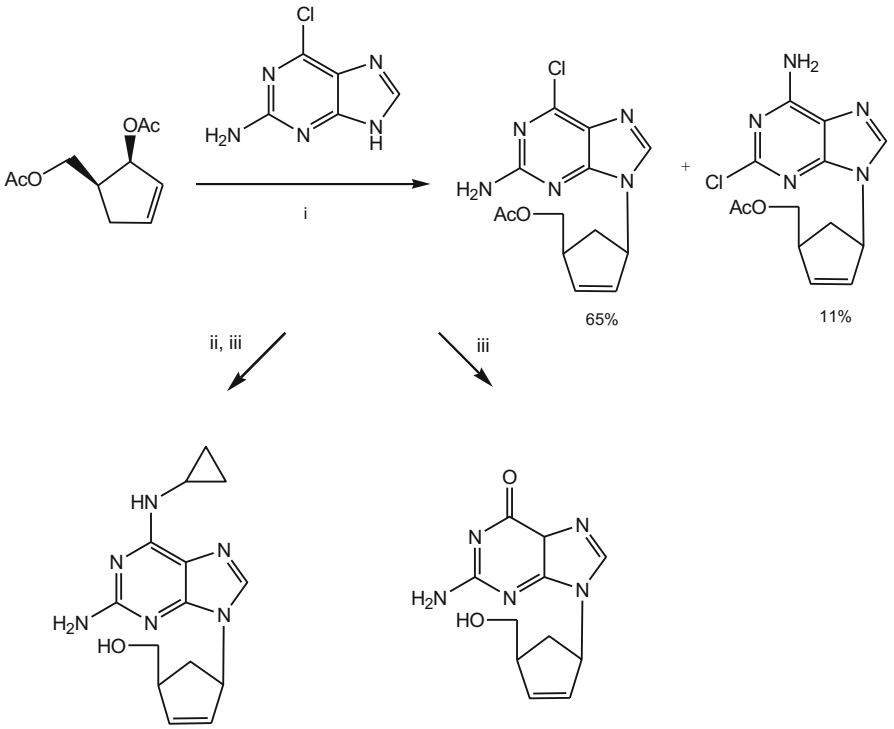


Scheme 4.60 Biosynthetic pathway of neplanocin A and aristeromycin

4.3.5 Enzymatic Synthesis

Likewise, carbocyclic nucleosides aristeromycin and neplanocin A can be biosynthetically prepared by using a mutant strain of *S. citricolor* as it is observed in Scheme 4.60.

The cyclopropylamino carbocyclic nucleosides (–)-abacavir is a potent anti-HIV with promising results on clinical trials [105]. An improved synthesis has been described by Crimmins et al. [106], involving the treatment of key carbocyclic 2-amino-6-chloropurine intermediate with cyclopropylamine producing Abacavir along its parent anti-HIV carbocyclic nucleoside (–)-Carbovir (Scheme 4.61).



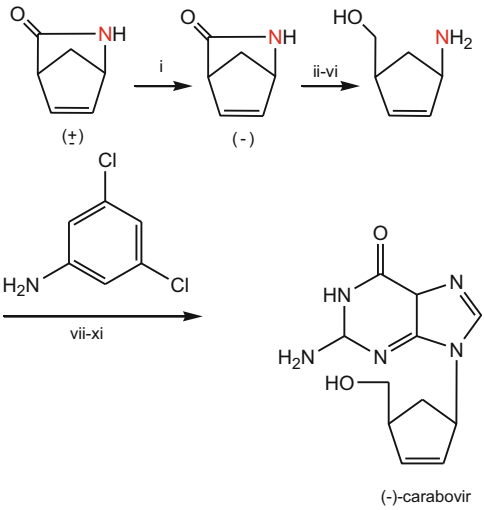
i) NaH, $Pd(PPh_3)_4$, 1:1 THF:DMSO. ii) cyclopropylamine, EtOH. iii) NaOH, H_2O.

Scheme 4.61 Synthesis of anti-HIV (−)-abacavir and (−)-carbovir

4.3.5.1 Base Ring Formation

Another useful strategy used for preparing carbocyclic nucleosides involves the use of intermediates in which the amino group is already attached to the sugar moiety and once the coupling reaction is achieved, a ring closure process takes place to generate the expected nucleoside. According to this procedure Roberts et al. [107] prepared the potent antiviral inhibitor (−)-carbovir which posses similar activity than AZT against HIV in MT-4 cells. Thus, the starting material (±)-2-azabiciclo [2.2.1] hept-5-en-3-one was submitted to microbial treatment with *Pseudomonas solanacearum* to provide enantiomerically pure (−) isomer. The enantiomerically pure carbocyclic amine was then conjugated to 2-amino-4,6-dichloropyrimidine to produce the carbocyclic precursor which was ultimately cyclized to provide the desired (−)-carbovir (Scheme 4.62).

Antileukemia carboxylic nucleoside Neplanocin A has been synthesized by Marquez et al., using the ring closure approach mentioned above. Thus, condensation of pyrimidine intermediate with isopropylideneaminocyclopentenediol furnished an



i) P.solanacearum NCIB 40249. ii HCl-H_2O. iii $(MeO)_2CMe_2$. iv) Ac_2O/Py. v) Ca $(BH_4)_2$/THF. vi) HCl-H_2O/EtOH. vii) PrNEt, nBuOH. viii) 4-Cl-$C_6H_4N_2$+Cl--AcOH, AcONa/H_2O. ix) Zn,AcOH/EtOH-H_2O. x) $(EtO)_3CH$/HCl. xi) NaOH/H_2O.

Scheme 4.62 Synthesis of (−)-carbovir

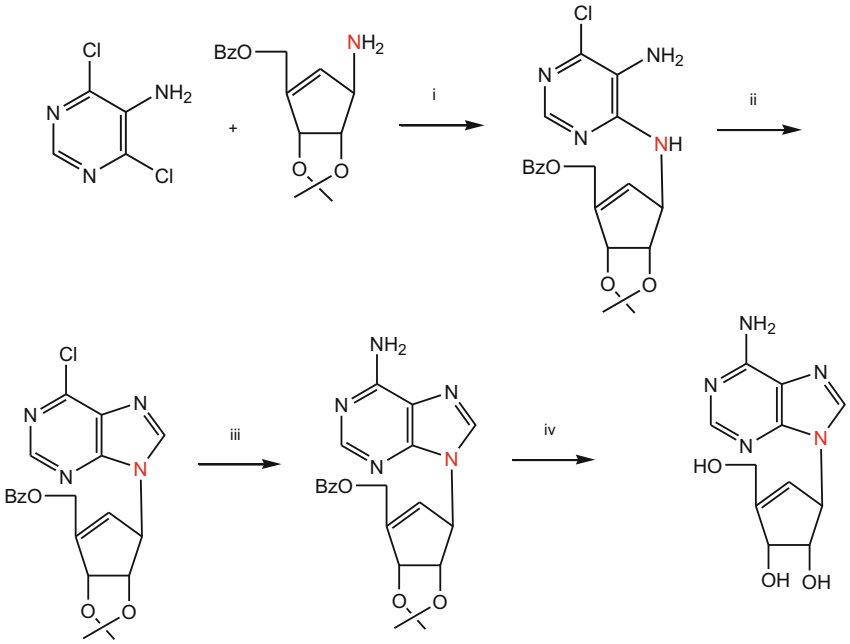
intermediate which was further cyclized to the purine base with triethylorthoformate. Final conversion to adenine ring with ammonia and protecting group removal gave rise to neplanocin A (Scheme 4.63) [108].

Likewise, this procedure was applied for the preparation of the close related pyrimidine analog by condensation of the previous carbocyclic amine with the unsaturated ether to produce the pyrimidine precursor who was transformed to thiopyrimidine and then to carbocyclic cytosine as it can be observed in Scheme 4.64. This compound has been found to be active against leukemia type L1210 in vivo [109].

An antiviral carbocyclic purine nucleoside was also reported [110] by following a ring closure step for purine formation. Condensation between pyrimidine intermediate and carbocyclic amine provided condensation product which is activated with diazonium salt for amino introduction. Ring closure was achieved with triethyl orthoformate in acid medium (Scheme 4.65).

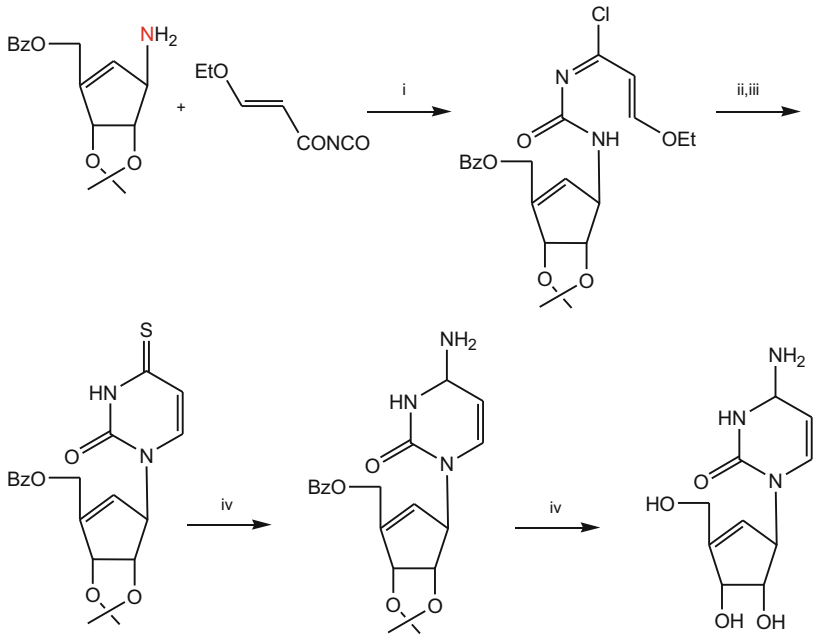
4.3.6 Carbocyclic C*-nucleosides*

This class of *C*-nucleosides in which a methylene group replaces the furan oxygen ring has not shown significant biological activity so far; however, there is an interest to synthesize *C*-nucleoside with natural heterocycle moieties in a stereocontrolled fashion. A recent stereocontrolled synthesis of carbocyclic *C*-nucleosides has been



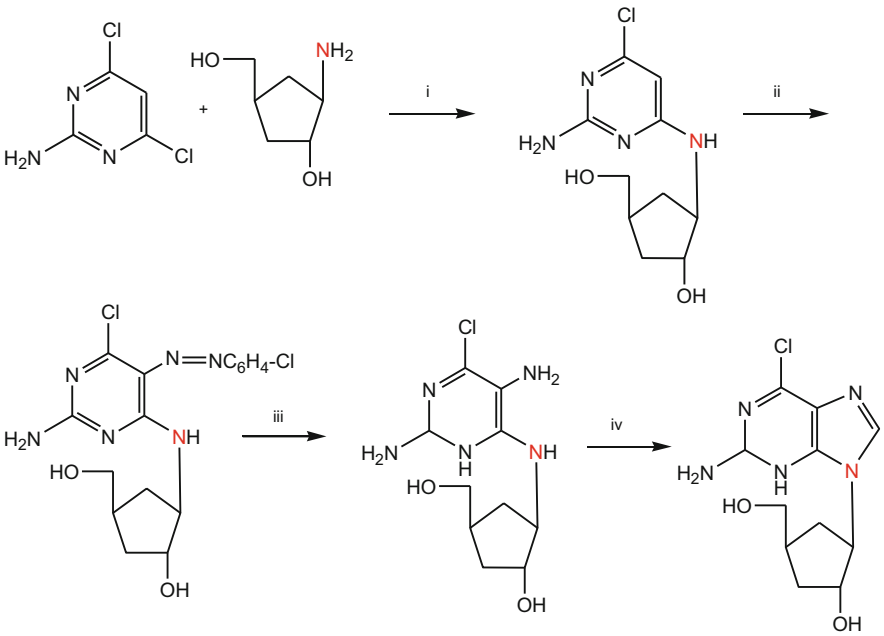
i) EtN_3/EtOH. ii) $HC(OEt)_3$, Ac_2O. ii) NH_3/MeOH. iii) BCl_3/CH_2Cl_2-MeOH

Scheme 4.63 Synthesis of neplanocin A



i) PhH. ii) DMF, NH_4OH. iii) Lawesson. iv) NH_3liq. v) a) BCl_3/CH_2Cl_2-MeOH. b) DowexH^+

Scheme 4.64 Synthesis of carbocyclic pyrimidine nucleoside



i) Et_3N/EtOH. ii) 4-Cl-$C_6H_4N_2^+Cl^-$, Na_2CO_3, AcOH/H_2O. iii) Zn/AcOH. iv) $CH(OEt)_3$-HCl/DMF.

Scheme 4.65 Ring closure approach for preparation of carbocyclic purine

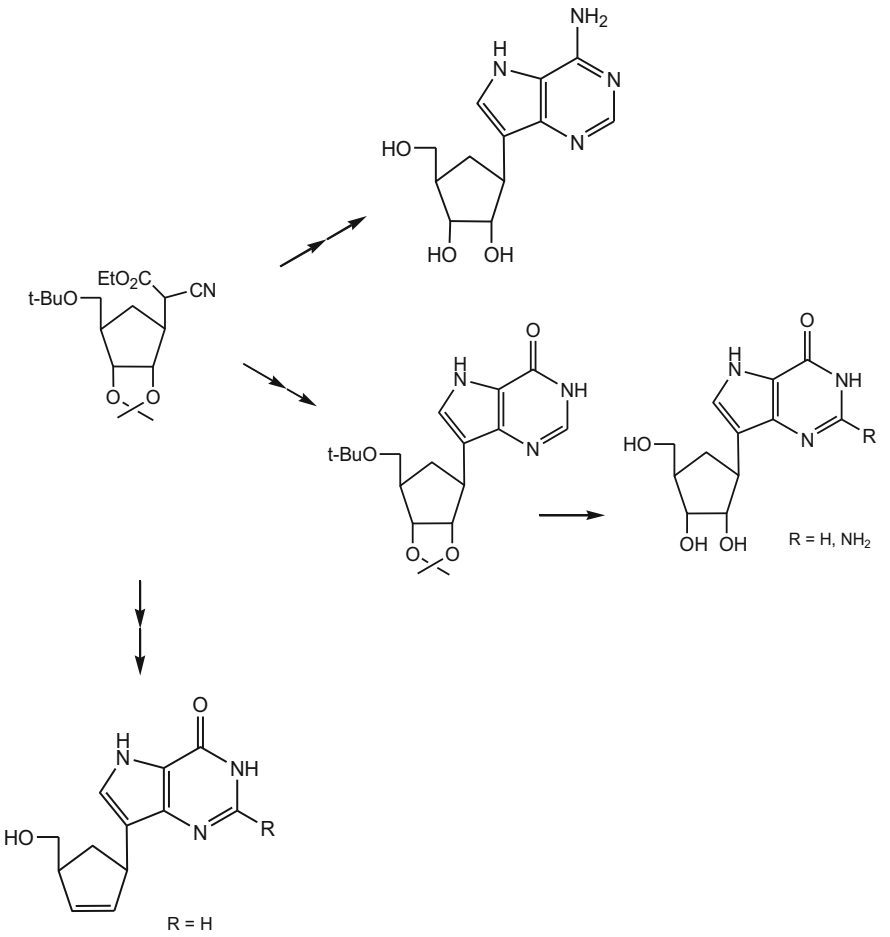
proposed involving as key starting material the cyano carbocyclic intermediate which was condensed to 9-deazapurine to produce saturated and unsaturated carbocyclic 9-deazapurine nucleosides (Scheme 4.66) [111].

4.4 Acyclic Nucleosides

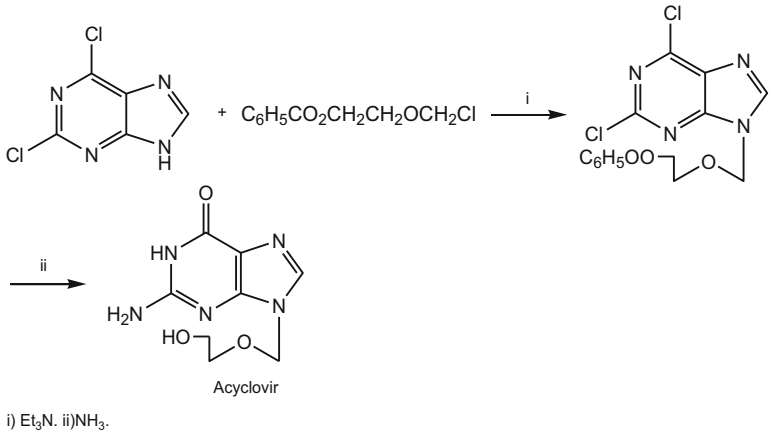
Since the discovery of acyclovir as an anti-herpes drug, important efforts have been made toward the synthesis of analogs of acyclovir and other acyclic nucleosides. A comprehensive review made by Chu and Cutler [112] summarizes the major achievements carried out for preparing acyclonucleosides defined as those heterocyclic compounds containing one or more hydroxyl groups on the alkyl side chain.

At least three representative synthesis of acyclovir have been made, the first by Schaeffer et al. [113] involving a condensation reaction of dichloropurine with ether chloride intermediate, and further purine transformation to generate 9-(2-hydroxyethoxymethyl)guanine (acyclovir) (Scheme 4.67).

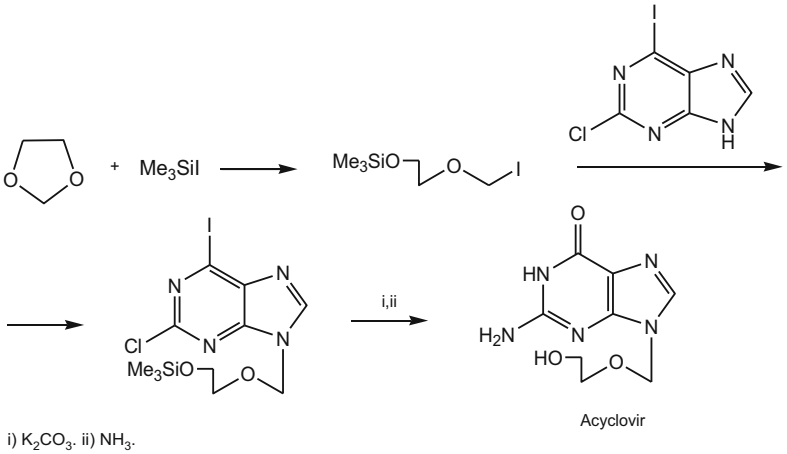
An improved version introduced by Barrio et al. [114, 115] consists in the initial reaction of 1,3-dioxolane with trimethylsilyl iodide to produce the side chain which was then condensed with the halogenated purine, to yield after hydrolysis and ammonolysis the target acyclovir (Scheme 4.68).



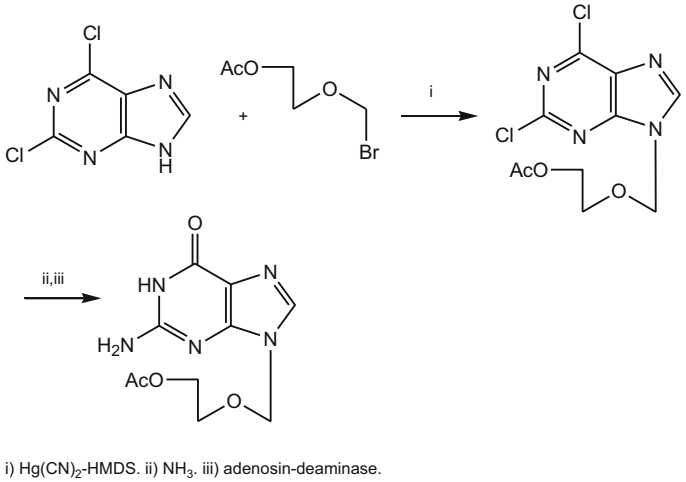
Scheme 4.66 Stereocontrolled syntheses of carbocyclic 9-deazapurine nucleosides



Scheme 4.67 First synthesis of acyclovir



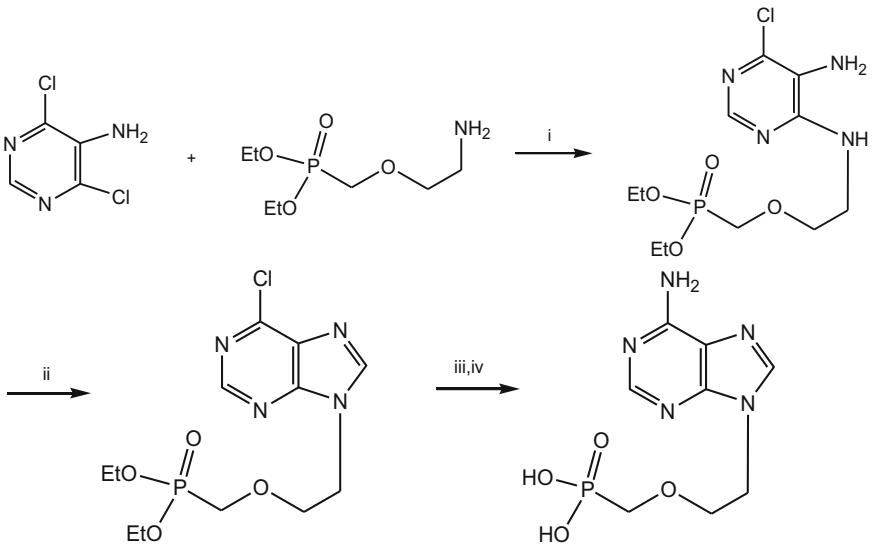
Scheme 4.68 Improved synthesis of acyclovir



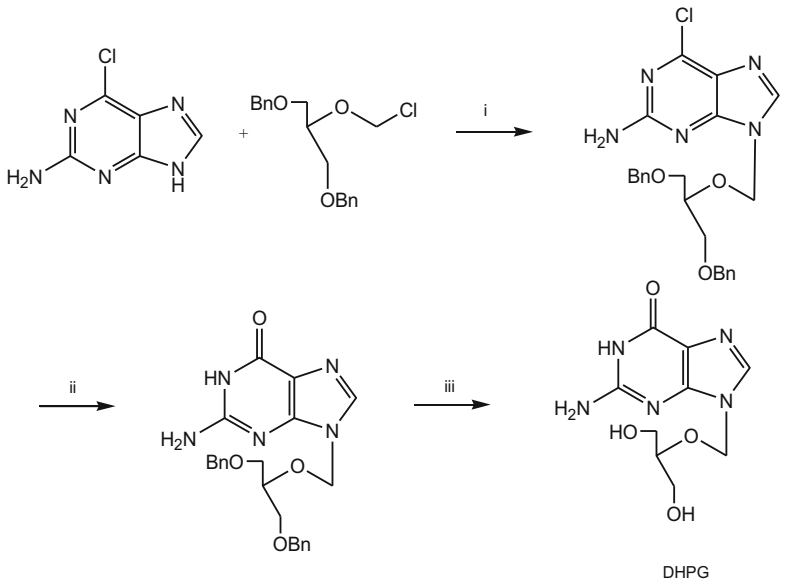
Scheme 4.69 Acyclovir synthesis

Robins and Hatfield [116] employed a chemoenzymatic approach for preparing acyclovir consisting initially in the use of mercury salts and hexamethyldisilane (HMDS) and in the final step an enzymatic conversion. Thus, the procedure involves the condensation between 2,6-dichloropurine and the bromoether, providing regioisomer N-7 shown in Scheme 4.69. Further amination and final transformation to guanine with the enzyme adenosin-deaminase produces the desired antiviral compound.

The phosphonate acyclic nucleoside 9-(2-phosphonomethoxyethyl)adenine (PMEA) was found to be a good antiviral analog with prolonged action [117]. A regio-defined synthesis base on the purine ring formation was described involving



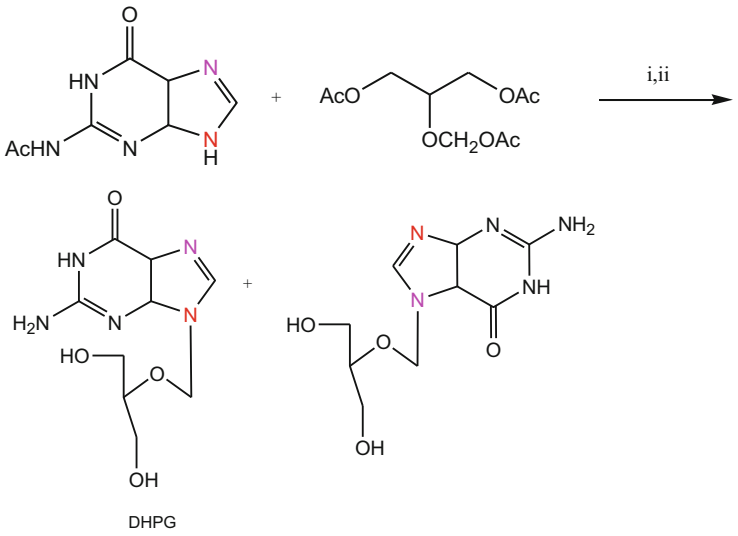
Scheme 4.70 Synthesis of phosphonate acyclic adenine PMEA



i) HMDS. ii) NaOMe, $HSCH_2CH_2OH$. iii) H_2, Pd-C

Scheme 4.71 Synthesis of antiviral acyclic nucleoside DHPG

the initial attachment of the phosphonate amine intermediate by nucleophilic substitution to the 5-amino-4,6-dichloropyrimidine base, and then ring formation followed by amination to produce the desired phosphonate acyclic adenine PMEA (Scheme 4.70) [118].



Scheme 4.72 Alternative synthesis of DHPG

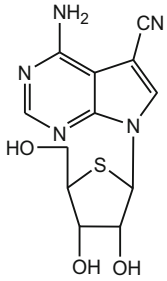
The effectiveness of acyclovir as antiviral drug encouraged different group to synthesize more potent acyclic analogs. As a result of this efforts, the acyclic nucleoside 9-[(1,3-dihydroxy-2-prpoxy)methyl]guanine (DHPG) [119] was prepared and tested as antiviral nucleoside, showing similar potency as acyclovir against simple herpes but stronger against encephalitis and vaginitis herpes.

Various report of DHPG were described, one of them involving the use of hexamethyldisilazane (HMDS) as condensing agent (Scheme 4.71) [112].

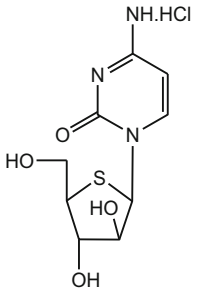
An alternative route for preparing DHPG involved the condensation reaction of acetylguanine base and triacetate derivative in the presence of ethanesulfonic acid, at temperatures ranging from 155 to 160 °C. As result two regioisomers were obtained from which one of those was converted to the desired antiviral compound Scheme 4.72 [112].

4.5 Thionucleosides

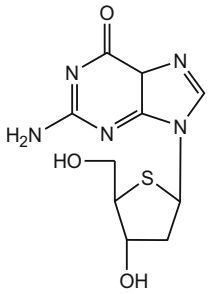
Nucleosides having the sugar ring oxygen replaced by sulfur are known as thionucleosides. The synthesis and therapeutic evaluation mainly as antiviral and anticancer drugs of these nucleoside mimics has been reviewed [120]. A comparative analysis of thionucleosides and nucleosides showed that sulfur replacement in some cases produced equivalent or higher potency [9, 121], and do not undergo enzymatic cleavage of the glycosidic bond, although it has been also observed increased toxicity as in the case of β-4′-thiothymidine [122] Some thionucleosides displaying antiviral and/or anticancer activity are shown in Scheme 4.73.



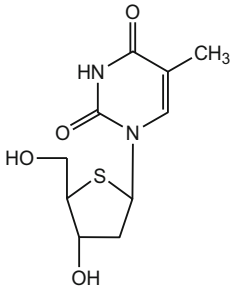
Thiotoyocamycin
Leukemia growth inhibitor



Thioarabinofuranosylcytosine
KB cell growth inhibitor

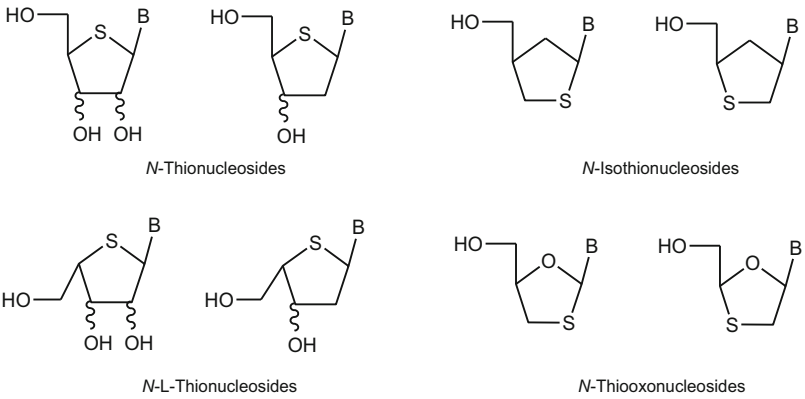


2'-Deoxy thioguanosine
Antiviral against HBV and HCMV



Thiothymidine
Carcinoma growth inhibitor

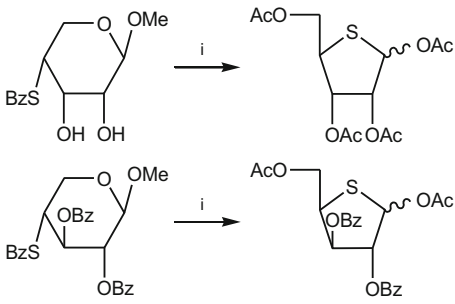
Scheme 4.73 Some active *N*-thionucleosides



Scheme 4.74 Classification of *N*-thionucleosides

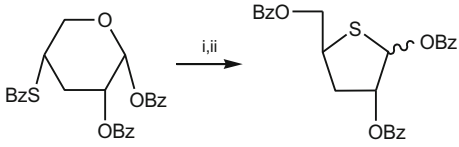
Based on their structural features *N*-thionucleosides defined also as thioribosyl sugars are classified into four groups (Scheme 4.74):

Scheme 4.75 Early synthesis of thioribofuranosyl derivatives



i) Ac_2O/AcOH, conc. H_2SO_4, 97%

Scheme 4.76 Preparation of benzoylated thioribofuranoside



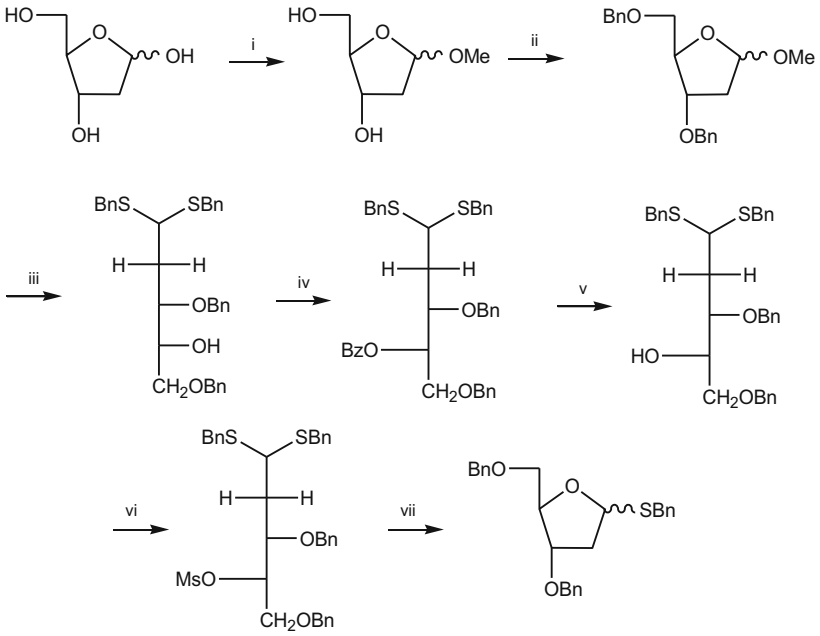
i) Na/aq. NH_3. ii) BzCl/Py

4.5.1 Preparation of Thioribofuranosyl Intermediates

A number of approaches oriented to replace or insert a sulfur atom instead or besides the cyclic oxygen into the ribose ring have been described. One of the earliest methods for preparing thioribosyl acetates was described by Reinst et al. [123, 124] involving as key steps the conversion of the 4-thiobenzoyl pyranoside into the thioribofuranosyl acetate (Scheme 4.75).

Short time later another report introduced the use of sodium in liquid ammonia followed by benzoylation to yield tribenzoylated thioribofuranoside as a mixture of anomers (α:β, 1:3) (Scheme 4.76) [125].

The thioribosyl derivative benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside has been prepared and used as glycosyl donor in various thionucleoside synthesis [125–127]. The synthesis started from 2-deoxy ribose which was transformed to the methylbenzyl derivative by following a standard procedure and then treated with benzylmercaptan in acid to produce the dithiobenzylated derivative. Next, was to invert the hydroxyl group at 4-position by using the Mitsunobu protocol to generate the intermediate with the desired stereochemistry. Final tosyl protection and NaI-$BaCO_3$ treatment provided the desired thiosugar (Scheme 4.77) [126].



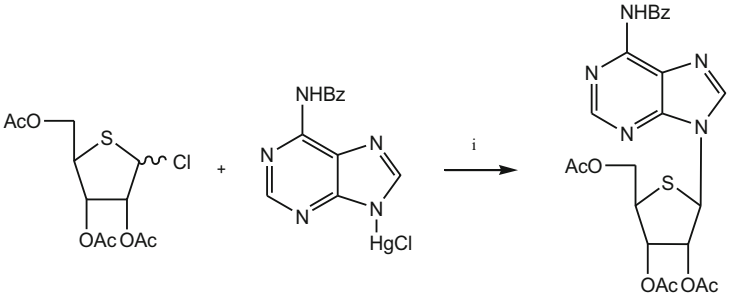
i) MeOH, HCl. ii) NaH, Bu_4NI, BnBr/THF. iii) BnSH,HCl. iv) PPh_3, $PhCO_2H$, DEAD/THF. v) NaOMe/MeOH. vi) MsCl/Py. vii) NaI, $BaCO_3$, acetone

Scheme 4.77 Synthesis of benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside

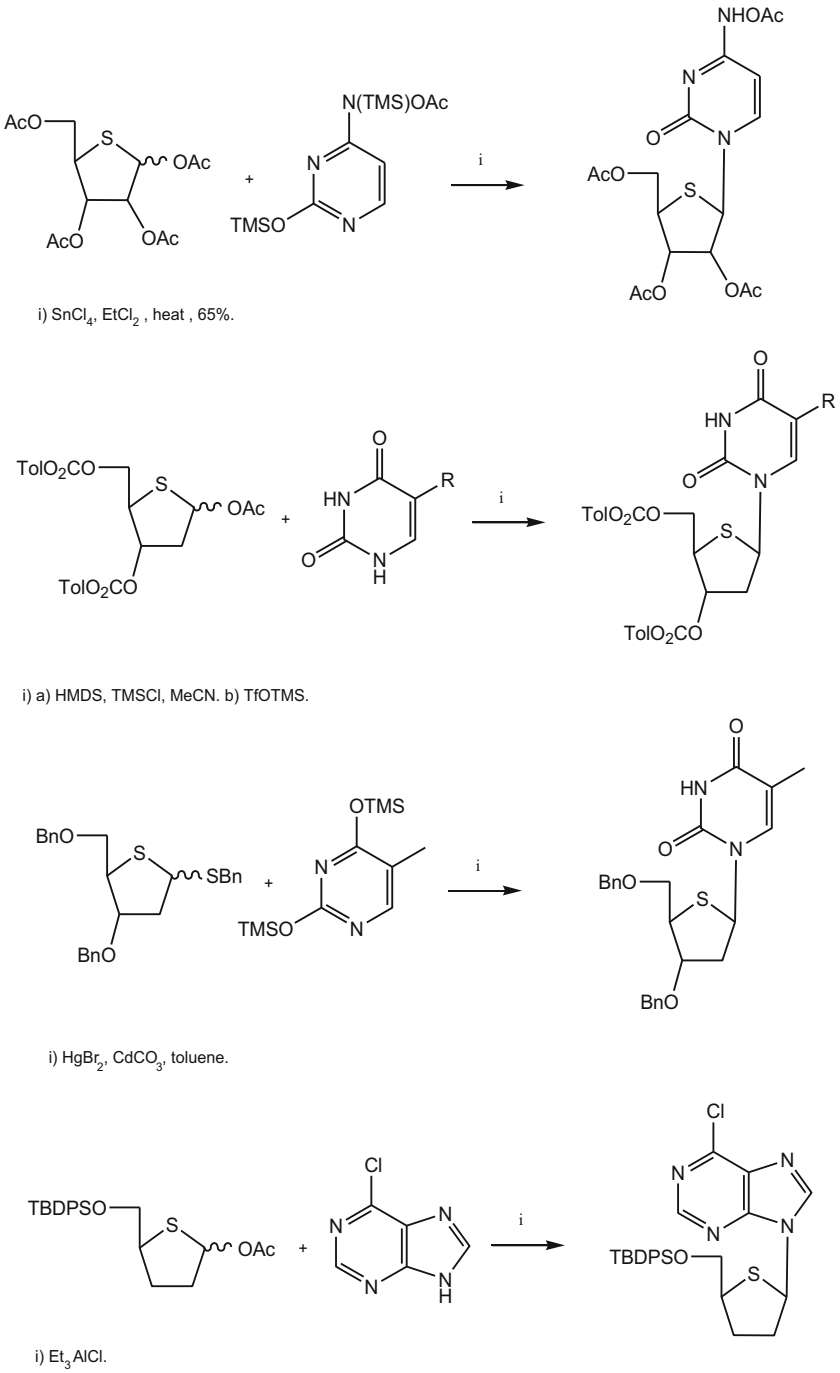
4.5.2 Glycosidic Bond Formation

The general methods for preparing *N*-thionucleosides are similar as for *N*-nucleosides; however, variations from slight to significant can be found specially in the preparation of four ring thietanocin or thiolane analogs [127, 128] Thus, according to a comprehensive review [120], the earliest reports for *N*-thionucleoside formation used chloromercury salt of purine and chlorine or benzoyl thioriboside as glycosyl donor, while more recently the silyl approach has been preferred (Scheme 4.78).

4.5.2.1 Chloromercuration Promoted Coupling Reactions

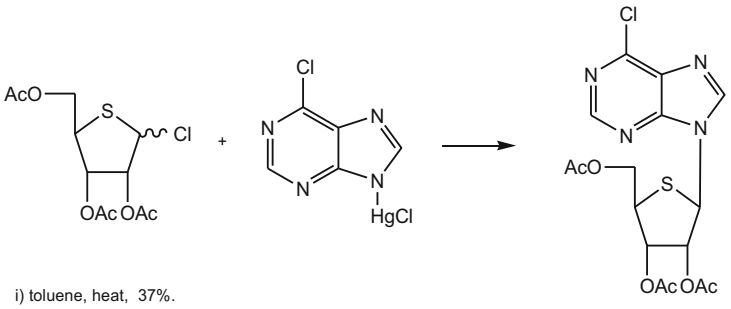


i) toluene



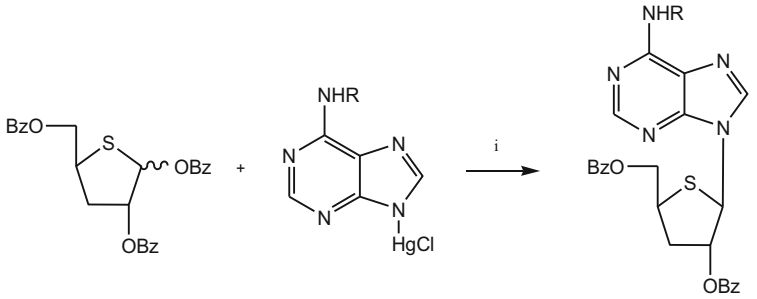
Scheme 4.78 Common glycosylation reactions for the preparation of thionucleosides [122, 129–132]

Ref. [123].



i) toluene, heat, 37%.

Ref. [129].

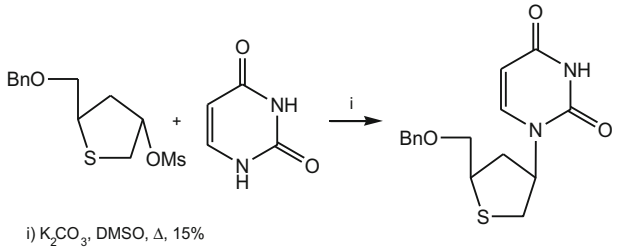


i)$TiCl_4$, $EtCl_2$, heat.

Ref. [130].

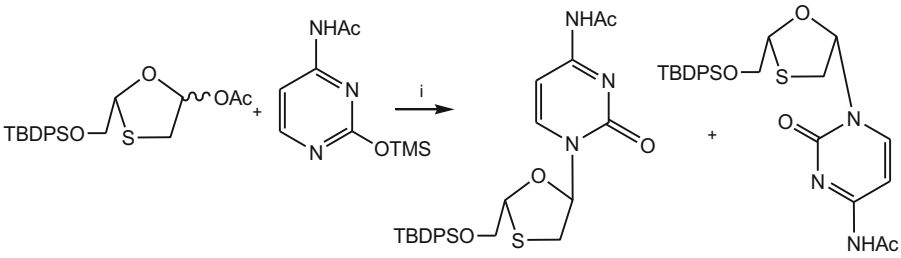
4.5.2.2 Silyl-Mediated Coupling Reactions

The preparation of potential anti-HIV *N*-isothionucleosides was described starting from glucose. The key coupling reaction proceeds in low yield between the pyrimidine base and the mesyl tetrahydrothiophene derivative under potassium conditions (Scheme 4.79) [133].



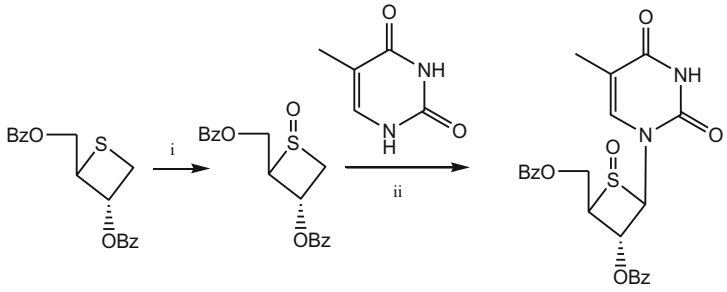
i) K_2CO_3, DMSO, Δ, 15%

Scheme 4.79 Preparation of *N*-isothionucleoside



i) TMSOTf, CH_2Cl_2, 64%

Scheme 4.80 Preparation of *N*-thioxonucleosides



i) TMSOTf, Et_3N, ZnI_2, toluene, 30 %.

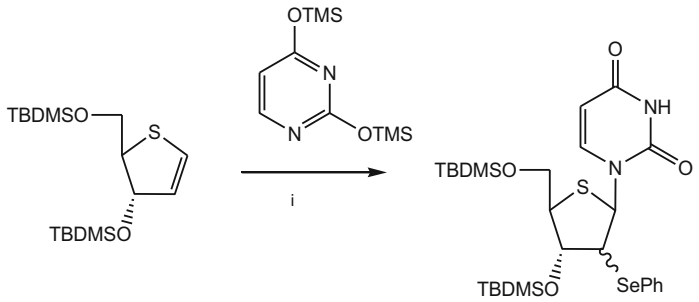
Scheme 4.81 Synthesis of thymidine thietane nucleoside

N-thioxonucleosides are another class of *N*-thionucleosides tested as anti-HIV agents. The conditions employed for performing the coupling reaction were TMSOTf as Lewis acid catalyst, providing a mixture of anomers (α:β, 1:2) in 64 % (Scheme 4.80) [134].

Thietane nucleoside was synthesized starting from the benzoyl thietane derivative which prior to the coupling reaction was treated with peroxide to produce the sulfoxide derivative. Then under Lewis acid conditions a Pummerer rearrangement process takes place to produce in the presence of thymine the expected thietane nucleoside (Scheme 4.81) [128].

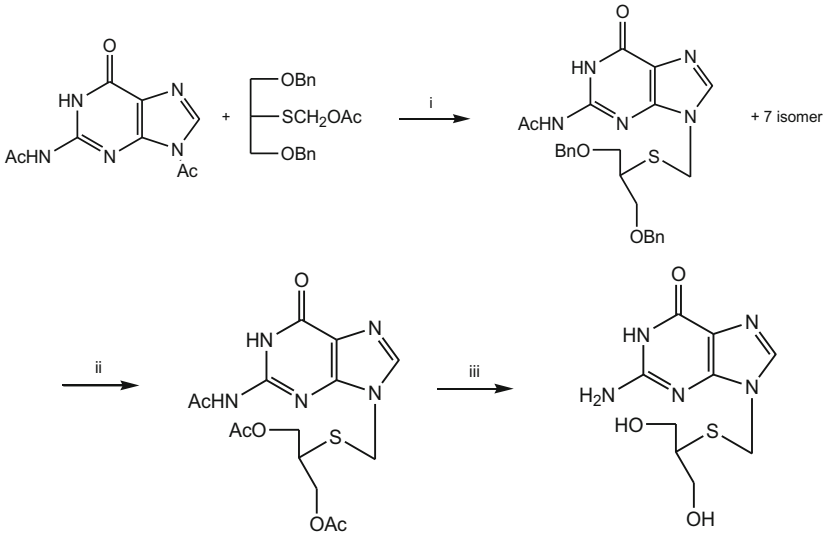
More recently the stereoselective synthesis of β-4′-thionucleosides based on electrophilic glycosilation of 4-thiofuranoid glycals has been described. Thus, the condensation of TBDMS-4-thioglycal with silylated uracil in the presence of PhSeCl as electrophile furnished thionucleosides in 88 % as a mixture of anomers (α:β; 1:4) (Scheme 4.82) [135].

The thio analog of antiviral DHPG with comparable activity to DHPG against HSV-1 and human cytomegalovirus was synthesized according to the scheme shown below (Scheme 4.83) [112].



i) PhSeCl 88 %.

Scheme 4.82 Synthesis β-4′-thionucleosides based on electrophilic glycosidation of 4-thiofuranoid glycols



i) $(p\text{-}NO_2C_6H_4)_2P(O)OH$. ii) $(C_2H_5)O\text{-}BF_3$,Ac_2O. iii) NH_3.

Scheme 4.83 Synthesis of thio analog of DHPG

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